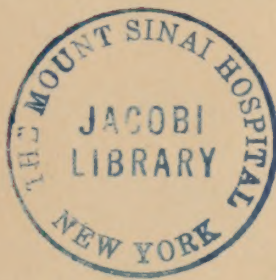




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CONTENTS

	PAGE
THE EDWARD GAMALIEL JANEWAY LECTURE. The Nature of Clinical and Experimental Arterial Hypertension. <i>Irvine H. Page, M.D.</i>	3
SUPPURATIVE AND NECROSUPPURATIVE BRONCHOPNEUMONIA IN CHILDREN. <i>Alexander Thomas, M.D.</i>	26
CLINICAL FEATURES, COURSE AND COMPLICATIONS OF SUPPURATIVE BRONCHOPNEUMONIA IN CHILDREN. <i>Herman Hennell, M.D.</i> ...	29
ROENTGEN FEATURES OF SUPPURATIVE BRONCHOPNEUMONIA. <i>Coleman B. Rabin, M.D.</i>	32
TREATMENT OF ACUTE SUPPURATIVE BRONCHOPNEUMONIA IN CHILDREN. <i>George J. Ginandes, M.D.</i>	37
THE TREATMENT OF AEROBIC PULMONARY ABSCESS. <i>Arthur S. W. Touroff, M.D.</i>	40
THE PLEURAL COMPLICATIONS OF ACUTE SUPPURATIVE AND NECROSUPPURATIVE BRONCHOPNEUMONIA <i>Harold Neuhoof, M.D.</i>	45
CLINICAL PATHOLOGICAL CONFERENCE.....	50
CLINICAL NEUROPATHOLOGICAL CONFERENCE.....	54
ABSTRACTS.....	61

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THE EDWARD GAMALIEL JANEWAY LECTURE

THE NATURE OF CLINICAL AND EXPERIMENTAL ARTERIAL HYPERTENSION¹

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Contemporary thought recognizes that arterial hypertension occurs in a variety of morbid states and that the stimulus which provokes it is not always the same. I say "contemporary" advisedly, because, until the last decade, observation of hypertension had largely been confined to description of its effects rather than investigation of its causes. It seems clear from the younger Janeway's writings that with, or/and possibly in spite of, his mastery of the purely nosological aspect of hypertension, his interests extended to include etiological enquiry. Indeed, his attempts with Carrel (1) to induce hypertension in animals by ligation of the renal artery foreshadowed experiments which were to be completed 25 years later. However, a defeatist attitude prevailed in the minds of other clinicians of his time which discouraged constructive investigation into the nature of these diseases. Hypertension and its sequelae had come to be considered by some as mere ravages of physiologic aging. Others obscured the issue by contenting themselves with diagnoses of heart failure, or uremia, or apoplexy. And so it was, until a method for the production of hypertension in animals which closely simulated essential and malignant hypertension in man was discovered by Goldblatt (2).

Of course it would be unfair to say that no work of significance was done before the production of experimental renal hypertension in 1934. Almost simultaneously with this discovery, and independently of it, there began an active investigation of the role of the nervous system in essential hypertension, which now bids fair to yield information of the greatest importance. Interest in the renal origin of hypertension has temporarily, I believe, eclipsed that in the part played by the nervous system. It might be well to recall that in 1929 severe hypertension without evident renal damage had been produced in animals by section of the carotid sinus and aortic depressor nerves.

It has proved convenient for purposes of presentation to divide the various syndromes in which hypertension occurs according to their pathogeneses into 1) nervous, 2) cardiovascular, 3) endocrine, and 4) renal

¹ Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York City, January 10, 1941.

groups. Since the mechanisms of these varied types of hypertension, except in rare instances, are by no means clear, this division must remain merely an aid and a stimulus to further investigation. Let me illustrate: removal of a pheochromocytoma causes the paroxysmal hypertension associated with it to disappear. With the demonstration by Beer, King and Prinzmetal (3) that adrenalin is detectable in the blood of these patients in significant amounts during the paroxysm and disappears when the tumor is removed, there seems little doubt that it is justifiable to class this variety of hypertension as endocrine. But the Wilms's tumors illustrate the converse state of affairs. Several years ago I was inclined, on the basis of published evidence, to include them among endocrine causes of hypertension. Subsequent studies showed that extracts of these tumors have no pressor activity. Their action in eliciting hypertension seems to be merely one of pressure on the parenchyma or pedicle of the kidney. Hence it now seems reasonable to classify the hypertension associated with Wilms's tumors as due to abnormalities of renal circulation. I shall avoid further discussion of this interesting phase of the problem of hypertension by inclusion of a classification of hypertension which we have found useful (4).

CLASSIFICATION OF HYPERTENSION

- | | |
|--|---|
| <p style="text-align: center;"><i>Renal</i></p> <p>a. Affections of vessels</p> <p>Arteriosclerosis</p> <p>Periarteritis nodosa</p> <p>Arteritis</p> <p>Anomaly</p> <p>Obstruction (tumors, aneurysm, arteriosclerosis, embolism, thrombosis)</p> <p>Thromboangiitis obliterans</p> <p>Visceral lupus erythematosus</p> <p>Wilms's tumor</p> <p>b. Affections of parenchyma</p> <p>Acute nephritis</p> <p>Chronic nephritis</p> <p>Pyelonephritis</p> <p>Hydronephrosis</p> <p>Polycystic disease</p> <p>Amyloidosis</p> <p>Infarcts</p> <p>Tumors</p> <p>Hypernephroma</p> <p>Ectopia</p> <p>Toxemia of pregnancy</p> <p>X-ray lesions</p> <p>Renal stones</p> <p>Hypogenesis</p> <p>Dystopia</p> | <p>c. Affections of perinephric structures</p> <p>Perinephritis</p> <p>Tumors</p> <p>Hematoma</p> <p>d. Affections of ureter</p> <p>Obstruction (pelvis, ureter, prostate, urethra)</p> <p>Pyelitis</p>
<p style="text-align: center;"><i>Cerebral</i></p> <p>Increased intracranial pressure (trauma, tumor, inflammation)</p> <p>Diencephalic stimulation</p> <p>Anxiety states</p> <p>Lesions of brain stem (ascending paralysis, poliomyelitis)</p>
<p style="text-align: center;"><i>Cardiovascular</i></p> <p>Heart failure</p> <p>Arterio-venous fistulae</p> <p>Angina pectoris</p> <p>Heart block</p> <p>Coarctation of aorta</p> <p>Atheromatosis</p> <p>Lead poisoning</p> <p>Polycythemia</p> |
|--|---|

Endocrine

Hyperthyroidism

Menopause (natural or artificial) †

Arrhenoblastoma

Pheochromocytoma

Adrenal carcinoma

Adrenal hyperplasia?

Cushing's syndrome (pituitary adenoma)

Pituitary basophilism?

Acromegaly

Thymic carcinoma

Unknown

Essential hypertension

Malignant hypertension

Production of Experimental Hypertension. Goldblatt, Lynch, Hanzal, and Summerville (2) were the first to produce chronic arterial hypertension without loss of urea clearance in animals by application of adjustable clamps to the main renal arteries.

A method of some theoretical and practical importance is the production of similar hypertension by compression of the parenchyma of the kidneys, either by the perinephric scar which results from application of silk or



FIG. 1. Cellophane perinephritis producing hypertension (242 mm. Hg) in a dog.

cellophane to the kidneys (5, 5a) or by preventing the hypertrophy which results when one kidney is removed (6). This calls attention to the possibility that compression of the renal parenchyma, whatever the cause—tumors, perinephric inflammatory reactions, or hematmata—may elicit clinical hypertension in some patients. Practically, the method is of value because of the simplicity and sureness with which hypertension is produced. A clinically dissimilar type had been produced by Koch and Mies (7) in rabbits by section of the carotid sinus and aortic depressor nerves. It might well be asked why the discovery of this latter type of hypertension has elicited relatively little interest.

The Mechanism of Elevated Blood Pressure. At least five separable factors control the level of arterial blood pressure. These are: 1) blood viscosity; 2) blood volume; 3) cardiac output; 4) cardiac augmentation; and 5) effective peripheral resistance. Let us now examine each of these factors and ascertain their importance in both clinical and experimental renal hypertension.

- 1) Blood viscosity and 2) blood volume. In animals with experimental hypertension both blood viscosity and volume are normal (8). This is apparently also true in essential hypertension although there is some disagreement in the reports in the literature.
- 3) Cardiac output. Cardiac output is normal in dogs with experimental hypertension and in patients with essential hypertension. The systolic hypertension of Grave's disease appears to constitute the chief exception to the rule of normal cardiac output in hypertension.
- 4) Cardiac augmentation. The increased force of the heart beat is familiar to all who have cared for patients with hypertension. Fahr (9) estimated that the increased work when the blood pressure was raised from 120 systolic and 80 diastolic to 240 systolic and 130 diastolic was about 95 per cent. The increase in work is nearly proportional to the elevation of systolic pressure and relatively much greater than the elevation of mean or diastolic pressure. Since the heart is only a specialized portion of the vascular tree, it might be expected that substances which augment the tone of the blood vessels would also augment the force of the heart beat. Thus cardiac augmentation must be one of the processes concerned in the genesis of hypertension. Whether augmentation is due to direct action of angiotonin on the heart muscle as appears to be the case in the isolated perfused cat's heart (Hill and Andrus (9a)), or is merely a reflection of Starling's law of the heart remains to be determined.
- 5) *Effective Peripheral Resistance*—The greatest fall in arterial pressure occurs in the arterioles (10) and in both patients and hypertensive dogs observation of the retinal arterioles shows that they are markedly constricted. But measurement has shown the blood flow in the arms to be either normal or elevated despite the elevated pressure. Since cardiac rate and output are not increased in hypertension, the elevated blood pressure must be due to cardiac augmentation plus increase in effective peripheral resistance. The nub of the problem of hypertension is to ascertain the cause of this change.

The anatomical site of the peripheral resistance has been the subject of active discussion. It has seemed reasonable from the plethysmographic studies of Prinzmetal and Wilson (11) and Pickering (12) that it is generalized and not greater or less in one particular area. This is based on the observation that blood flow in the forearm of hypertensives is no greater than normal. Abramson (13) has restudied the problem with what appears to be a more refined technique and concludes that in hypertensives it is 1.7 times greater than normal. From these results it appears that some area such as the splanchnic may in fact offer more resistance than other portions of the vascular system. Since there is disagreement on the observation, it is not possible on the basis of this evidence to decide which view is correct.

The evidence is clear that in most patients with hypertension the kidneys interpose marked resistance to the flow of blood. Since about 30 per cent of the cardiac output may flow through the kidneys in each minute, they must constitute an important part of the effective peripheral resistance. The remainder of the splanchnic area also appears to contribute importantly to the maintenance of elevated peripheral resistance.

It is of course impossible to determine the effective peripheral resistance by random sampling in various vascular areas of the body. It may, however, be calculated roughly by the formula of Bazett, Cotton, Laplace and Scott (14):

$$\text{Effective peripheral resistance (R)} = \frac{\text{Mean pressure}}{\text{Cardiac output per square meter surface}}$$

The equation has been shown to be fairly adequate for basal conditions. Inherent is the assumption that blood pressures determined from the brachial artery are representative of the whole arterial tree, an assumption only partially true in the horizontal and even less true in the vertical position. Wiggers (15) points out that, as a rule, increase in mean pressure is accompanied by augmentation of effective resistance but some patients with extreme elevation of pressure have no greater peripheral resistance than others with moderate hypertension. He also finds that the diminution of vascular distensibility so commonly found in the large vessels in hypertension does not affect the peripheral resistance significantly. It is evident that the problem of peripheral resistance needs to be more extensively investigated and the results related to the clinical type of hypertension.

The Nervous System and Peripheral Resistance. The care of patients with hypertension must have convinced most physicians that, whether or not the nervous system is directly responsible for hypertension, at least in many cases it plays a highly demonstrative role. Their irritability, aggressiveness, combativeness, insomnia, all point to a disturbed psyche. An interesting somatic expression of this is seen in patients exhibiting the hypertensive diencephalic syndrome (16), in whom crying, blushing, tachycardia, perspiration, and hyperperistalsis occur without adequate external cause. This points to lack of integration in the diencephalic centers.

Operations on the nervous system such as the anterior nerve root section, the supra- and infra-diaphragmatic splanchnic nerve sections, with removal of many of the ganglia, and total sympathectomy have shown beyond doubt that the arterial pressure can be profoundly altered by these procedures (17 to 21). Whether or not it stays down for prolonged periods at least the reduction is sufficiently prolonged to demonstrate the effect of such operations. The cause of the fall in blood pressure is not certainly known. It is not due to increased blood flow through the kidneys and

probably is in part the result of inadequate filling of the heart incident to the denervation of the splanchnic area (22).

It may be recalled that I stated that severe hypertension could be produced by section of the carotid sinus and the aortic depressor nerves. Injection of kaolin into the cisterna magna also produces hypertension. The clinical counterpart of the former type of experimental hypertension has not been recognized and much evidence points against the view that the carotid sinus mechanism itself is deranged in essential hypertension. Except in certain rare examples, it is doubtful if the latter type occurs at all frequently. Nevertheless, hypertension of nervous origin should not be forgotten in our haste to blame the kidneys.

I have leaned toward the view that the nervous system in many cases plays a subsidiary, though important, role in the mechanism of hypertension, in both maintaining the blood vessels in a reactive state as well as actually contributing toward vasoconstriction by vasomotor impulses. It is possible that in some cases it initiates the steps leading to hypertension of humoral nature.

Systematic examination of the effect of ablation of special portions of the nervous system on the arterial pressure has been carried out on animals with experimental hypertension in which renal denervation, anterior spinal nerve root section, splanchnic nerve section, and even total sympathectomy combined with cardiac denervation are without perceptible influence on arterial blood pressure. So drastic a procedure as pithing does not abolish the hypertension though it may reduce it. These experiments strengthen the belief that the nervous system plays at most only a small part in the genesis of experimental renal hypertension. The erect posture with its attendant dependence upon rapid splanchnic vasomotor readjustments and the high organization of central nervous control in human beings forbid direct transfer of results obtained from operations on the nervous systems of animals to an application in diseases of human beings. Nevertheless, these experiments suggest that in many cases of essential hypertension at least the nervous system is not the primary genetic agent.

The Endocrine System and Increased Peripheral Resistance. Patients with essential hypertension do not commonly exhibit obvious marks of endocrine dysfunction. But in animals, ablation experiments clearly demonstrate the importance of the endocrine system. Let us start with the "master gland," the pituitary, and determine the effect of its removal in experimental hypertension (23). Hypophysectomy leads to a relatively slow fall in blood pressure. The extent of the fall and its maintenance appear to depend on the extent of the somatic changes associated with hypophysectomy. That this operation does not interfere with a primary mechanism of hypertension is evident from the fact that increased stimulation of the renal pressor system by further reducing the caliber of the renal artery leads to an additional rise in blood pressure.

The mechanism by which the hypophysis exerts an effect on blood pressure is not known. The plausible suggestion has been made that its action is an indirect one by supplying adrenocorticotrophic hormone to stimulate the adrenal cortex.

Color is lent to this belief by the demonstration that excision of the adrenal cortex has a profoundly depressing action on the arterial pressure of hypertensive dogs, yet mild hypertension persists if the animals are properly treated with cortical extract and salt (24 to 26). The fact that hypertension remains at all demonstrates that the adrenals are not alone vital to the maintenance of elevated arterial pressure. The part they play is not known. It is perhaps significant that adrenalectomy in the absence of replacement therapy causes dogs to become refractory to renin (27).

The thyroid gland, pancreas, and gonads apparently do not participate importantly in the genesis of hypertension, for their removal in hyper-

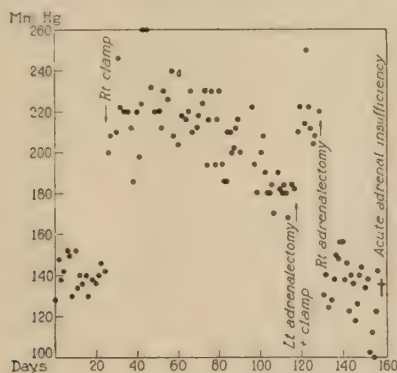


FIG. 2. Effect of adrenalectomy on arterial blood pressure of a hypertensive dog.

tensive animals does not alter the blood pressure. Similar lack of effect is observed in human hypertensives when the thyroid or gonads are removed.

The evidence suggests that participation of the endocrine system in the genesis of many cases of hypertension is, like that of the nervous system, important though probably subsidiary to other primary causes.

A Humoral Mechanism Elevating Arterial Pressure. If a search is to be made for a substance which is thought to cause hypertension, it is important to seek one whose characteristics are consonant with those to be anticipated from knowledge of the physiology of hypertension. Therefore, 1) this substance must elevate arterial pressure without reduction in peripheral blood flow; 2) it must constrict the efferent arterioles in the kidneys and thus maintain the rate of glomerular filtration while tending to decrease renal blood flow; 3) it must cause cardiac augmentation; 4) it must be present in the peripheral blood of hypertensive patients; 5) it must not cause the hypertensive animal to become refractory after re-

peated injections (tachyphylaxis). Let us now examine contemporary evidence to see whether such a substance has been found. At the outset it is clear that the usual pressor substances, such as adrenalin and pitressin do not fulfill the requirements. Since systematic investigation of the various systems in animals with experimental renal hypertension demonstrates the subsidiary part played by all but the humoral system, it was natural that study of the latter system should begin with the pressor substance contained in the crude extracts of kidneys prepared by Tigerstedt and Bergmann (1898). When these extracts were injected intravenously into intact animals, the active principle contained in them, so-called renin, caused a prolonged rise in blood pressure. But further injection elicited either only a slight rise or none at all. The animals were said to be tachy-

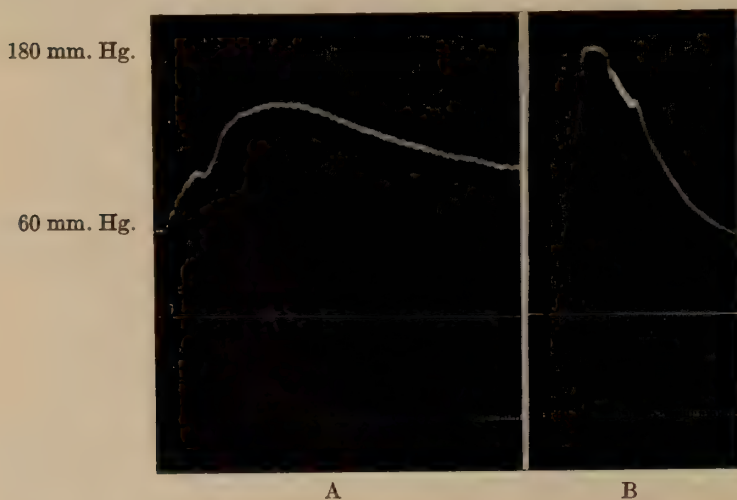


FIG. 3. Effect of injection of renin and angiotonin on arterial blood pressure of a pithed cat. A (left) = renin. B (right) = angiotonin.

phylactic. For these and other reasons it did not appear to many that renin could play any part in the genesis of hypertension.

Stepwise purification of renin by Helmer (28) with simultaneous assay of the fractions on both intact animals and isolated perfused rabbits' ears led to the important observation that the more active the preparation became in the intact animal, the less active it was in the isolated ear perfused with Ringer's solution (29). A point was reached where no constriction whatever resulted when renin was perfused through the isolated ear, yet the same renin caused a powerful rise of blood pressure in intact animals.

These observations could lead to but one conclusion, namely, that some substance was contained in blood which was not contained in Ringer's

solution. This was confirmed by adding blood to renin and after incubation of ten minutes injecting the mixture into the Ringer's solution perfusing the ear. Immediate and powerful vasoconstriction resulted. Further study showed that the activating effect was produced by the pseudo-globulin fraction of plasma. While there is good evidence that the reaction between renin and this fraction of plasma is enzymatic in nature, it is not conclusively proved. For this reason we called the plasma pseudo-globulin fraction, "renin-activator." It seemed unwise to crystallize prematurely the concept of this reaction by calling renin the enzyme and the pseudo-globulin fraction the substrate, though this has been our working hypothesis.

Since it was recognized that renin was no simple pressor substance but that it worked only in conjunction with its specific activator, it became possible to study in more detail the mechanism of its physiological action. Clearly, if the activator contained in the blood could be neutralized or



FIG. 4. Crystals of angiotonin picrate.

exhausted, renin could not exert its pressor action. It was shown that the activator had its origin in the liver, for hepatectomy in dogs caused it to disappear within several hours. But a much simpler way was found by injecting an excess of renin into the blood. Such exhaustion of the renin-activator supply is part of the phenomenon known as tachyphylaxis, i.e., lack of pressor response after repeated injections of renin (30).

Let us now return to the interesting phenomenon just described, in which it was found that in isolated organs perfused with Ringer's solution, renin causes no vasoconstriction unless renin-activator is incubated with it. This pointed indubitably to the fact that the reaction product was the vasoactive material. The isolation of this substance was much simplified by demonstrating that it was thermostable. Boiling destroyed both renin and renin-activator and left the pressor substance in solution. By a fairly elaborate series of chemical manipulations this substance was crystallized and shown to be a strong pressor agent (31, 32). I shall not discuss what

is already known of the chemical structure of this substance, called angiotonin, except to say that it is unlike any known pressor substance.

After the demonstration of the reaction between renin and renin-activator by Kohlstaedt, Helmer and Page (29), Muñoz, Braun-Menendez, Fasciolo and Leloir (33) independently found pressor activity in filtrates prepared by incubating renin with renin-activator and boiling the solution. They did not isolate and crystallize the pressor substance, but showed that it had many of the physiological properties of angiotonin.

Our evidence suggests that angiotonin is an intermediate rather than an end product because if angiotonin or renin is allowed to continue to react with serum or plasma, the final product has no pressor action (32). At least two possibilities present themselves to explain this result. Angiotonin may be an intermediate in a series of reactions which ultimately lead to its destruction, i.e., $\text{renin} + \text{renin-activator} \rightarrow \text{angiotonin} + \text{angiotonin-activator} \rightarrow \text{vaso-inactive substance}$. Angiotonin may be destroyed by an enzyme contained in plasma and kidneys. The latter suggestion seems the more probable because contact of angiotonin with plasma leads to its *slow* destruction, the temperature coefficient is low, and circulation of angiotonin through the living kidneys results in a vaso-inactive effluent from the kidneys.

Physiological Considerations of Angiotonin. It would now seem justifiable to examine some of the physiological properties of angiotonin to ascertain whether they fulfill the criteria proposed for a substance which could be concerned in the mechanism of hypertension, both experimental and clinical.

1) Angiotonin causes marked elevation of arterial pressure both in human beings and in animals without causing blanching, fall in skin temperature or decrease in peripheral blood flow. This means that the chief site of constriction is proximal to the capillaries, i.e., in the arterioles, and that the force of the heart's beat has augmented to overcome the increased peripheral resistance.

The effect of the injection of angiotonin is particularly well illustrated in the transparent chambers introduced into the rabbit's ear. This allows microscopic examination of the arterioles, capillaries and veins. Such investigation demonstrates that in comparing equi-pressor amounts of angiotonin and adrenalin, the former causes little interference with the flow of blood in the capillaries while the latter causes complete bloodlessness (34). It will be necessary to study the effect of angiotonin on other vascular areas such as the muscle and brain before the relative importance of peripheral resistance and cardiac augmentation can be determined.

2) The most characteristic intrarenal hemodynamic change in patients with hypertension has been shown by Smith, Goldring and Chasis (35) to be maintenance of glomerular filtration rate and reduction of renal blood flow. This can, as they point out, only be due to constriction of the

effluent glomerular artery. Clinically, this is reflected in these patients in early loss of ability to concentrate urine with maintenance of inulin and urea clearance. Normal human beings filter from 16 to 20 per cent of the plasma water into the renal tubules, whereas many hypertensives filter more than 20 and even 30 or 40 per cent. This must be due to increased intraglomerular pressure. The increased intraglomerular pressure in turn could be due either to dilatation of the afferent glomerular arterioles or to constriction of the efferent arterioles. If the former occurred,

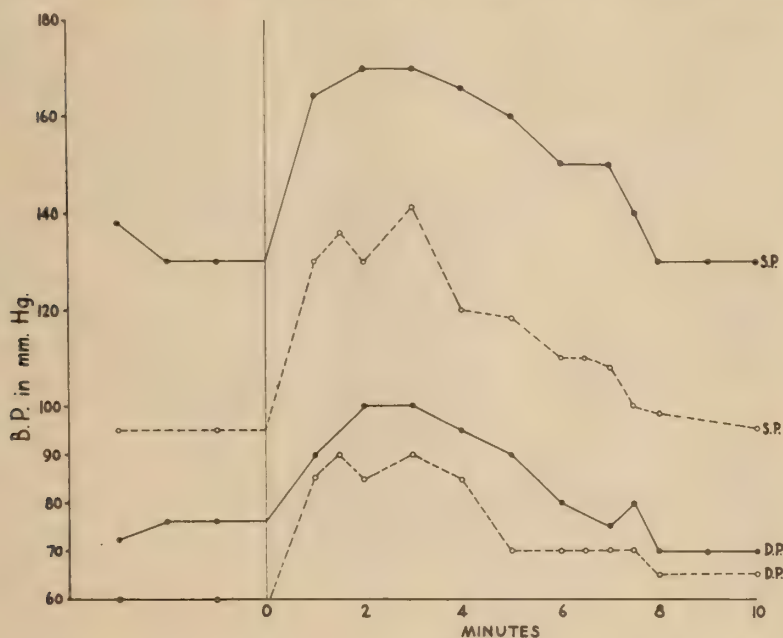


FIG. 5. Effects of single intravenous injections of angiotonin on arterial blood pressures in two patients.

Patient 1. ●—●, dose injected 0.6 cc.

Patient 2. •- -•, dose injected 1.0 cc. Ordinate: Systolic (S.P.) and diastolic (D.P.); blood pressure in mm. Hg. Abscissa: time in minutes.

blood flow in hypertensive patients would be increased, which is certainly not the case. It is concluded, therefore, that efferent arteriolar constriction prevails. Clinically, an important corollary of the efferent arteriolar constriction in hypertension is the fact that urea clearance, which depends upon the rate of glomerular filtration, does not vary directly with renal blood flow under such conditions.

A matter of great interest is Coreoran's demonstration (36) that angiotonin produces severe efferent arteriolar constriction in both dogs and in human beings, reproducing the characteristic intrarenal hemodynamic state in essential hypertension. With renin the effect in dogs is more

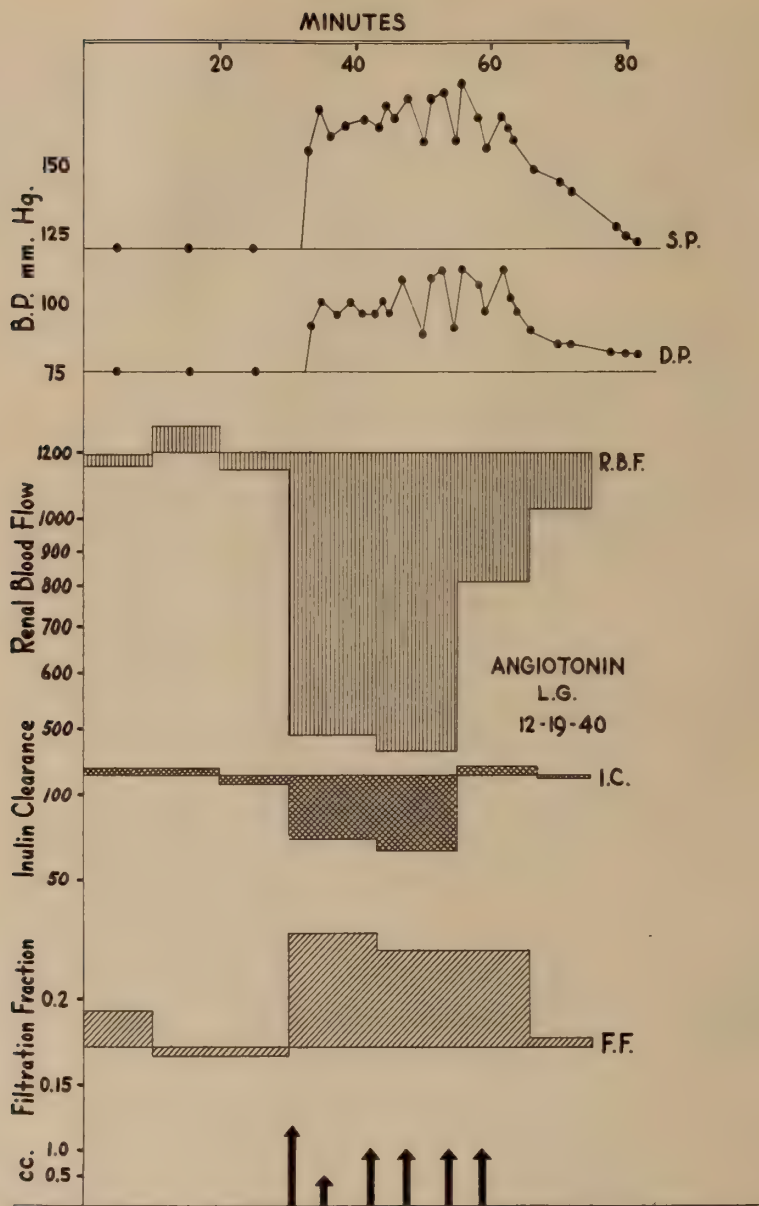


FIG. 6. Effects of infusion of angiotonin on arterial blood pressure, renal blood flow, inulin clearance and filtration fraction in patient L. G. Ordinates from above downwards: arterial systolic (S.P.) and diastolic (D.P.) blood pressures; effective renal blood flow (R.B.F.) in cc. per min.; inulin clearance (I.C.) in cc. per min.; filtration fraction (inulin/diodrast clearance ratio, F.F.); cc. indicates volumes of initial intravenous injection of angiotonin and of subsequent injections into the infusing fluid. Effective renal blood flow, inulin clearance and filtration fraction are plotted semilogarithmically. Abscissa: time in minutes.

prolonged than with angiotonin, but qualitatively the results are the same. These results have been confirmed in dogs by thermostromuhr measurements (37), and by direct observation of the circulation in the transilluminated frog's kidney (38).

3) The amplitude of the heart beat is markedly increased in perfused cats' hearts when angiotonin is added, according to Hill and Andrus (39).

4) I stated as the fourth criterion that the pressor substance must be present in the peripheral blood. This is a matter which is not easy to prove. We must get ahead of our story, in order to make clear the steps involved in this study. Removal of both kidneys in animals greatly increases their sensitivity to angiotonin. The enhanced sensitivity is reflected in the blood, for if blood from such "arenal" animals is employed as the perfusing fluid in a rabbit's ear, addition of either angiotonin or renin causes much more powerful vasoconstriction than when normal blood is used. These, then, would be the conditions under which any increase in angiotonin-like substance in the peripheral blood would be most easily detected.

Perfusion of rabbits' ears with "arenal" blood has shown (40) that addition of a small amount (0.2 cc.) of plasma from normal animals produced little or no vasoconstriction, whereas plasma from hypertensive dogs or patients caused definite constriction. Plasma of hypertensives could thus be readily distinguished from that of normotensives.

This vasoconstrictor is not renin, because addition of renin-activator does not increase its power to cause vasoconstriction when perfused through the rabbit's ear. Injection of renin into an animal causes it to appear in the blood. In other words, it seems to originate from renin under the circumstances usual for the production of angiotonin. Its vasoconstrictor action is enhanced when perfused with "arenal" blood (a property not shared by pitressin, adrenalin, tyramine or methyl-guanadine) and it occurs in dogs and patients with hypertension but not in normotensives. It is for these reasons we refer to this peripheral vasoconstrictor as "angiotonin-like," and it seems to me cogent evidence that a substance is in fact present in the blood, bathing the heart and blood vessels, which could cause cardiac augmentation as well as arteriolar constriction. This is further strengthened by the demonstration that transfusion of large amounts of blood from hypertensive to normal dogs causes a rise of arterial pressure in the recipient (41). Recent observations suggest that this peripheral pressor substance may not be angiotonin itself but something closely allied to it. Possibly it is a substance resulting from the interaction of angiotonin with its activator (42).

5) All observers are agreed that repeated injections of renin at short intervals cause the animal to become refractory. This phenomenon has been called tachyphylaxis. The phenomenon is in part, as we discussed before, due to exhaustion of renin-activator. Part is due, as we shall see

later, to the occurrence of an inhibitor originating in the kidneys. But tachyphylaxis to renin develops much more rapidly than to angiotonin. With single doses of angiotonin the arterial pressure may be elevated 30 mm. Hg. many times in short order without appreciable tachyphylaxis occurring. Since removal of the kidneys all but abolishes tachyphylaxis to angiotonin, we have believed that some similar circumstance might exist in hypertensives, that is, some lesion of the kidneys which causes the animal to approach from this aspect the condition of the "arenal" animal. I shall not discuss the evidence for this any further because it is incomplete, and, in my view, not altogether convincing.

It will be seen that for the most part angiotonin is able to reproduce those criteria set out as being characteristic of the physiology of hypertension. It would, however, be rash indeed to claim that this evidence is sufficient to establish angiotonin as the cause of hypertension. All that seems justifiable is that it appears to be the most likely substance yet found. Objection to renin as the responsible agent has been voiced (43, 44). Whether equally cogent objections apply to angiotonin remains for further study.

Liberation of Renin from the Kidneys and the Conditions under which This Occurs. Observations of renal clearances of phenol red, inulin, creatinine and urea, as well as determinations of renal blood flow by indirect methods have shown that in some instances hypertension may be induced by partial constriction of the renal artery without a decrease in renal blood flow (45). It is, of course, not easy to attain this point of balance in operative application of metal clamps and it goes almost without saying that severe experimental hypertension is usually associated with renal ischemia. However, since it may be assumed that the more severe types of experimental hypertension are in some measure the result of the liberation of higher concentrations of angiotonin into the blood, it follows that the renal ischemia which has been demonstrated under such conditions is in part the result rather than the cause of the hypertensive process. These observations and the conclusions reached from them call into question the assumption that experimental renal hypertension due to compression of the renal artery or renal parenchyma is the result of renal ischemia.

In casting about for another explanation of the origin of renal hypertension it was necessary to select conditions of study which were as simple and controllable as possible. The isolated perfused dog's kidney from the point of view of controllability is satisfactory. That the preparation is simple in the sense that the conditions are physiological seems unlikely. Nevertheless, under proper, and I may say elaborate conditions of perfusion, Kohlstaedt (46) was able to show that no renin is liberated from kidneys perfused at normal blood pressure and flow. But if the blood flow was maintained and the pulse pressure reduced, renin appeared in the

renal vein in abundance. From this it may be concluded that the stimulus to the liberation of renin from the kidneys was reduction of pulse pressure, or in other words, the partial conversion of pulsatile to a continuous flow of blood.

Renin is a large molecular protein contained in the tubular cells of the kidneys. The conditions for its liberation would therefore doubtless involve some increase in permeability of the cell membranes of these cells. What changes occur when continuous flow is used instead of pulsatile flow in perfusing organs are not known. It is certain, however, that organs become edematous and cease functioning much more quickly when con-

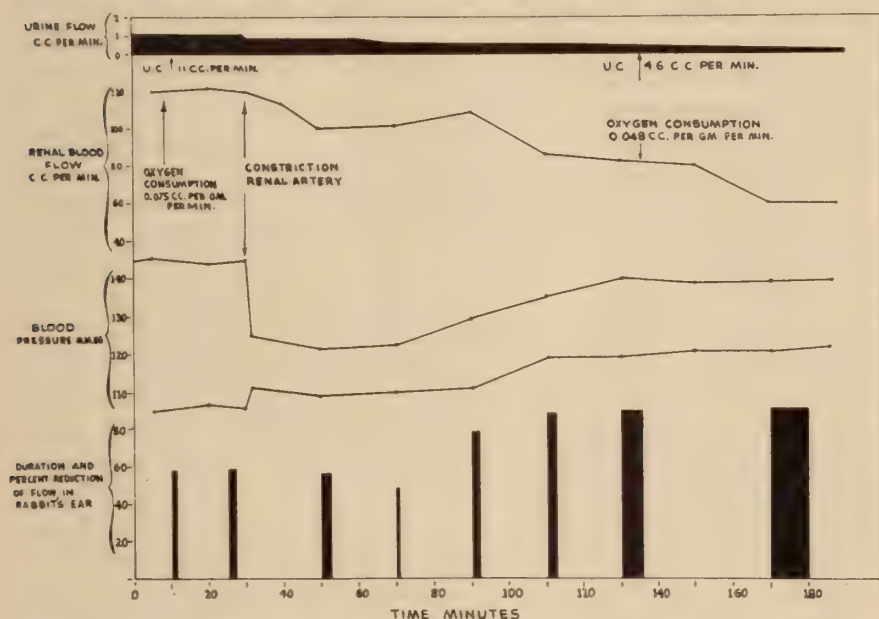


FIG. 7. Effect of reduction of pulse pressure on the renin secretion of an isolated perfused dog's kidney. The black columns represent the amount of renin secreted.

tinuous flow is used. Whatever the reasons, it seems possible that the change resulting from reduction in pulse pressure in the kidneys leads to increase in permeability and liberation of renin into the renal vein. It is obvious that severe reduction of blood flow through the renal artery would lead not only to hypertension but to atrophy of the kidneys, whereas characteristically atrophy does not occur in the early stages of essential hypertension.

It can be equally well demonstrated (47) that renin is liberated from the kidneys of unanesthetized dogs with experimental hypertension by taking samples of blood from the veins of kidneys which have been explanted into the dog's flank. Normal dogs' kidneys do not liberate renin in amounts detectable by our present methods.

Blood from the renal veins of many patients with essential hypertension have been examined and found to be rich in renin.

We are now in a position to make a reasonable guess as to the mechanism of the renin-angiotonin vasopressor system. Reduction of pulse pressure in the kidneys leads to liberation of renin by increasing the permeability of the tubular cells. This renin combines, probably enzymatically, with the renin-activator fraction of the blood to form angiotonin. Hence blood in the renal vein will contain a mixture of renin and a small amount of angiotonin. As the renin circulates, more of it is converted to angiotonin. By the time the blood has reached the heart and arterioles, most of it has been converted to angiotonin. Angiotonin in the presence of its own activator causes peripheral arteriolar constriction, efferent arteriolar constriction in the kidneys, and cardiac augmentation, resulting in arterial hypertension.

Inhibition of the Vasopressor System. Bilateral nephrectomy produces a remarkable increase in sensitivity of animals to both angiotonin and renin. Reflection on these observations must lead to the notion that in removing the kidneys either one has removed the organs necessary for the excretion of pressor substances (48), or that the kidneys in some manner destroy (49) or neutralize the pressor substance (50 a, b, c).

Several investigators have diligently studied the urine of patients with hypertension to demonstrate the occurrence of characteristic pressor substances. According to some of the published reports these efforts have been successful, but unfortunately the results have never been satisfactorily confirmed. Others have believed that lack of pressor substance in the urine might be characteristic of hypertensive patients, and this has not seemed unreasonable. Again, the results have lacked confirmation.

Our own investigations (51) along this line show the pitfalls with which one is faced. Extraction of urine by several methods showed that the extracts in all but one of a group of normal control subjects contained large amounts of pressor substance. On the other hand, extracts of the urine in a group of hypertensive patients in the hospital showed none. It would have been reasonable to suppose that the hypertensive patients retained the pressor substance and therefore had hypertension, whereas, the normotensive person excreted it and hence did not. Unfortunately this attractive theory was shattered by the demonstration by Helmer that the pressor substance which we had crystallized from the urine was pure nicotine. In retrospect it was clear that the patients in the hospital were not allowed to smoke, while all but one of the controls did so.

In short, no substance has as yet been demonstrated in the urine which appears to have any relationship with arterial hypertension. This suggests that it is more reasonable to believe that the kidneys either destroy the pressor substance or secrete some neutralizing substance. The demonstration that when one renal artery is clamped or the parenchyma enclosed

in a perinephric scar and the remaining normal kidney removed, the blood pressure rises much more quickly and severely than if the normal kidney remains intact, seems to be best interpreted in this light. It is important next to decide whether the kidneys destroy the pressor substance by some intrinsic metabolic process or whether they excrete a substance which neutralizes its action. If blood from an "arenal" dog is used as the perfusing medium for a rabbit's ear, it is found that the vessels of the ear constrict much more vigorously to the same amount of angiotonin than if normal blood is used (42). This experiment points to the presence of some substance in normal blood which dampens the vasoconstrictor properties of angiotonin. It is not present in the "arenal" blood.

Further demonstration of the fact that an inhibitor is contained in normal blood is furnished by experiments in which the sensitivity of "arenal" dogs to angiotonin was tested before and after large transfusions of normal blood (42). After the transfusion, the "arenal" dog responded much as a normal one, suggesting the transfer of some substance contained in blood from a dog with kidneys intact which is not present in the "arenal" dog.

There is other evidence that an inhibitor is secreted by the kidneys (52), but sufficient has been given to show that an attempt to extract this substance from kidneys would be profitable.

Attempts to extract such an inhibitor have been successful both in the hands of Grollman, Williams and Harrison (53) and in our own (54). The evidence available indicates that we are dealing with the same active principle as that reported shortly before by Harrison, Grollman and Williams. Our work was done entirely independently and was based on different reasoning. The two groups are now collaborating toward a further solution of the problem. It is of real interest that Schroeder (55) has recently reported that tyrosinase prepared from mushrooms will also reduce arterial pressure in animals with experimental hypertension and in human beings with essential hypertension.

Preparation of Extracts Containing Inhibitor. Chemical methods for the preparation of kidney extracts have been published by both Grollman, Williams and Harrison (55) and our group (54), and need not be given in detail. Suffice it to say that they consist essentially of extraction of ground kidneys with acid water, heating to 56°C., and fractional precipitation of the filtrate with ammonium sulfate. The fraction precipitated between 0.25 and 0.6 saturation contains the greatest amount of active substance. Precipitation is repeated and the ammonium sulfate removed by dialysis.

Effect of Kidney Extracts on Hypertensive Dogs and Rats. Injection of extract equivalent to 100 grams of kidney per kilogram per day for 4 to 6 days into hypertensive dogs lowers the mean arterial pressure from 50 to 100 mm. Hg. After several days the pressure usually rises again and in several weeks may have attained its original level. Strangely, in some of

the dogs the blood pressure remains low. They are "cured" in the sense that even after many months the pressure does not rise, but whether this is a direct effect of the extract or some indirect one is not known.

If excessive doses of extract are given, the pressure falls sharply over a period of 24 to 48 hours and the animals exhibit a shock-like syndrome well described by Williams, Grollman and Harrison (56). The extremities become cold, and tachycardia, profound weakness, loss of appetite, and vomiting occur. The pressure continues to fall and the animal dies with oliguria or anuria and marked retention of urinary excretory products in the blood.



FIG. 8. The effect of injection of inhibitor on the mean arterial pressure of a hypertensive dog (Dog 391).

Treatment of dogs in which the malignant syndrome has supervened is one of the most dramatic evidences of the activity of renal extracts. This syndrome in dogs is usually heralded by the occurrence of bloody diarrhea and weakness. It is soon followed by partial or complete blindness. Examination of the ocular fundi shows that large areas of the retina are detached and, if the nerve head is visible, papilledema is evident. Blood may fill both chambers of the eye. Usually those animals die in several days unless treated. If treatment is begun before the animal is moribund, the clinical change is remarkable. Within 24 to 48 hours it appears almost normal and regression of the eye ground changes have clearly occurred. The treatment has been discontinued in some animals and in a few the malignant syndrome has reappeared and again treated with success. In others, complete recovery from the syndrome appears to have occurred.

The results have been about the same in rats as in dogs.

The effect of these extracts on renal function is naturally a matter of the greatest importance. For if it could be shown that they abolish the change which we have come to believe as characteristic of essential hypertension, it would add to the notion that the renal extracts were, in fact, part of the angiotonin-renin vasopressor system.

Corcoran and I (57) have studied this subject with the aid of the inulin, diodrast, and phenol red clearances in both dogs and patients. These

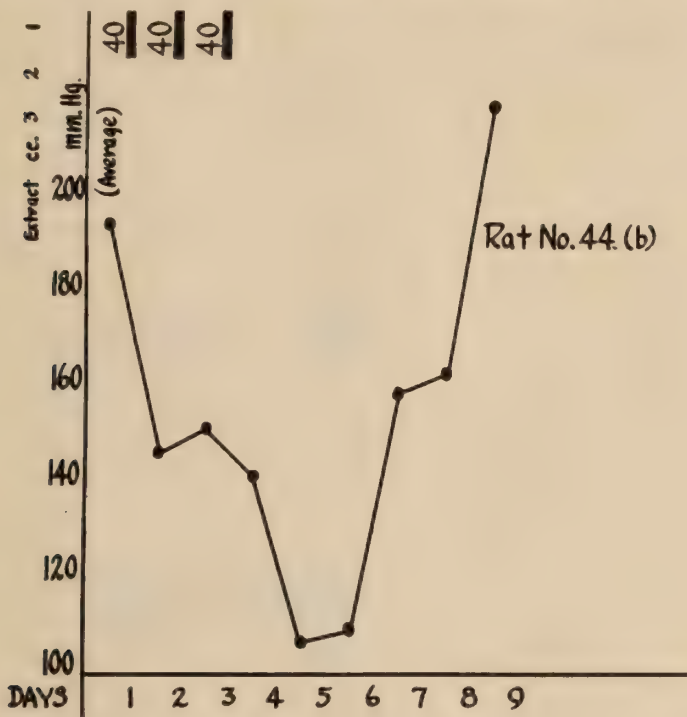


FIG. 9. The effect on arterial blood pressure of a hypertensive rat of injection of inhibitor. The black columns at the top of the diagram represent the amount of whole kidney in grams extracted to produce the inhibitor.

results show that with decrease in arterial pressure due to injection of extract, there occurs a rise in renal blood flow which is accompanied by a decrease in filtration fraction. This is interpreted as indicating a specific relaxing effect of the inhibitor on the efferent arteriole and a consequent probable improvement in the nutrition of the renal cells.

It is interesting to note, since it suggests that the renal pressor system may not function alone during morbid states, that injection of extracts containing the inhibitor in normal dogs also results in relaxation of the efferent arterioles and increased renal blood flow (58). The renal action of the inhibitor may explain the mechanism of the anuria and nitrogen

retention which follows the administration of excessive doses in experimentally hypertensive animals, for in such animals relaxation of the efferent arterioles in the presence of restrictions to intra-renal arterial pressure may result in cessation of glomerular filtration at a time when blood still courses through the kidney.

Effect of Inhibitor on Patients. Seventeen patients with hypertension have now been treated by injections with kidney extract. In some cases local reactions to the extract have been quite severe but transient. Sys-

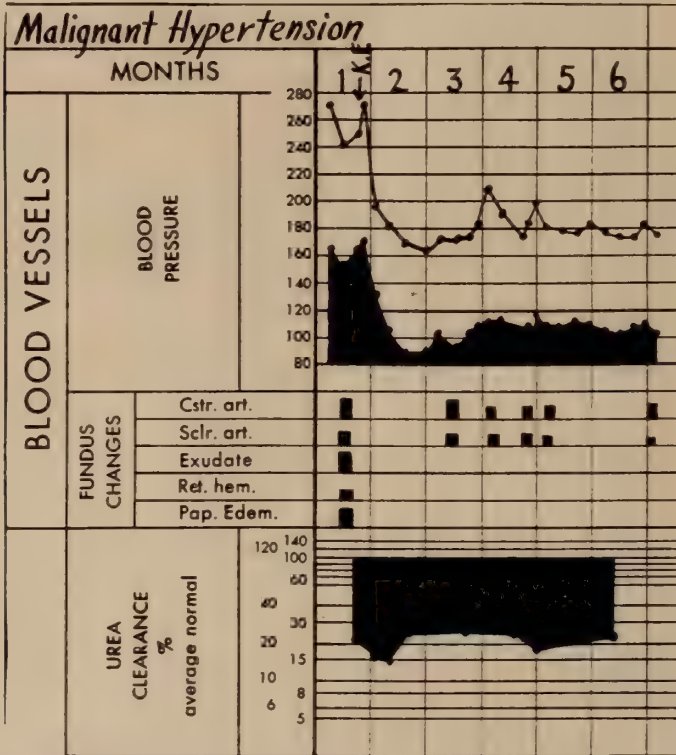


FIG. 10. The effect of injection of inhibitor on the arterial blood pressure and eye-grounds of a patient with malignant hypertension.

temic reactions in which the blood pressure falls precipitously have also been observed from time to time. There seems to be little regularity in their appearance. We believe them to be anaphylactoid because they may not be as intense when the patients are desensitized by repeated injections of extract and histamine.

Amounts of extract equivalent roughly to 1000 grams of original whole kidney are injected daily. Usually after a week or more a noticeable drop in blood pressure has occurred, but two months may be required before it is normal. It is necessary to continue the injections at least every other

day because the arterial pressure rises to its initial height within a week or more.

Perhaps the most striking clinical changes in patients with essential hypertension has been disappearance of headaches, precordial pain and shortness of breath when these were present. Their feeling of well-being is evident. Since many of these patients have few or no symptoms, the change in blood pressure would seem to be a mere academic achievement. Unfortunately this scarcely squares with the facts of the clinical history of this subtle disease.

The most dramatic results have been observed in patients suffering from malignant hypertension. Nine of these patients have now been treated. Vision has rapidly returned with accompanying regression of eye ground changes. Decreased constriction of the glomerular efferent arterioles and increased renal blood flow have repeatedly followed the effective administration of these renal extracts. Urea clearance has increased in some instances and, in others, has decreased. However, as noted above, urea clearance does not have a simple relation to the rate of renal blood flow in hypertension and it is therefore significant that the fall of urea clearance which may follow the administration of such extracts is merely an expression of relaxation of the constricted efferent arterioles and, paradoxically, has been accompanied by increased renal blood flow. Since increase of renal blood flow should improve the nutrition of the ischemic renal cells, it is significant that an improvement in the capacity of these cells to do work by concentrating urine has usually followed treatment with inhibitor. When convulsions have been present they have not recurred. Appetite improves and the general rapid down-hill trend seems to be arrested.

These results are based on the experience of only a year with extracts which have varied widely, some good, some bad, yet on the whole we feel the results encouraging. As time has passed the extracts have become more pure and more potent and the results in the patient have been correspondingly more regular and definite. That arterial blood pressure can be lowered in both man and animals and kept down for months or years seems beyond doubt, but how much ultimate benefit this will be to the patient receiving these extracts, time and work alone can tell. Administration of renal extracts is not yet to be considered a practical treatment.

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The following series of papers which deal with suppurative bronchopneumonia in children and which were presented as a symposium before the Pediatric Section of the Academy of Medicine on October 10, 1940 is the result of a joint effort of the Thoracic Group of The Mount Sinai Hospital. Essentially, there is summarized the view of the Group concerning the suppurative pneumonias as encountered in children. There is no claim for originality, although a number of observations which have been made do not appear to have been reported in the literature. The general purpose has been to present the views which have been arrived at on the basis of clinical and roentgenological observations made over a period of years. In particular the intention has been to indicate the clinical implications of the disease as encountered in children.

HAROLD NEUFELD, M.D.

SUPPURATIVE AND NECROSUPPURATIVE BRONCHOPNEUMONIA IN CHILDREN

PATHOLOGY AND PATHOGENESIS

ALEXANDER THOMAS, M.D.

Suppurative bronchopneumonia may be said to include those cases of bronchopneumonia in which suppuration of the lung forms part of the pathological picture. The suppuration may range from microscopic foci up to multiple large abscesses. An analysis of the various types of cases indicates that suppurative pneumonia can be divided into a number of general groups, based on the pathology.

The first group comprises those cases of bronchopneumonia in which the suppurative element is relatively minor and incidental. The bronchopneumonia itself may be mild, as when death is due to some extra-thoracic cause, in which case the suppuration is usually limited to scattered microscopic or miliary foci. Or, the pneumonia itself may be diffuse and fulminating, as in influenza, measles, pertussis, or the terminal bronchopneumonia of marantic infants. In the latter the suppuration may be more marked, with the formation of many small abscesses, but is still relatively inconspicuous and insignificant both pathologically and clinically, except in those rare instances in which the rupture of one of these abscesses leads to a suppurative pleuritis. From the frequency with which this incidental element of suppuration is found at post-mortem examination in cases of bronchopneumonia, one may assume that many such cases recover without clinical evidence of the existence of suppuration.

The second group includes the cases of bronchopneumonia in which suppuration, both pathologically and clinically, plays an important, and

frequently dominant, part. In this group our present views of the pathology are based on the clinical, x-ray and operative findings, and the gross pathological studies in the cases coming to autopsy. It is possible that further study will modify these views. In these cases the microscopic foci of suppuration are widespread within well defined areas, with the alveoli and bronchioles filled with pus throughout the area of bronchopneumonia. Many gross abscesses are formed by the destruction of the walls of alveoli and bronchi and the coalescence of these suppurative foci. One of the features of these cases is that healing and restitution to normal is most likely to be incomplete, resulting in a chronic interstitial pneumonitis with fibrosis, or a chronic bronchiectasis, or both.

In a certain number of these foregoing cases, there is another important element in addition to the suppuration, namely necrosis. These cases of acute suppurative pneumonic infection in which necrosis is a gross and obvious element have been designated as necrosuppurative bronchopneumonia. This distinctive term is used in order to emphasize the presence of necrosis, because the necrosis forms such a striking part of the pathological picture and plays such an important part in determining the evolution of the lesion.

In these necrosuppurative cases the infection involves one or more bronchopulmonary segments, that is, a secondary bronchus with its tributary bronchioles and pulmonary parenchyma (1). With the development of marked necrosis in a case of suppurative pneumonia the evolution of the lesion results in the formation of an abscess. This is called "non-putrid segmental pulmonary abscess."

Two types of necrosuppurative bronchopneumonia with the formation of abscess can be distinguished. There is the group in which the abscess, which is frequently multiple, is found surrounded by a significant and often diffuse area of pneumonitis. In other words, these are cases in which necrosis has occurred in a certain area or areas of an active suppurative pneumonia, with the formation of abscesses in the midst of this active infection.

In the other type the abscess formation dominates the pathological picture while the surrounding zone of pneumonitis is very limited. Any individual case of necrosuppurative pneumonia may during its development pass from the first to the second type, and conversely, a case in which a large abscess with a minimal surrounding pneumonitis has developed may become a more diffuse lesion through a spread of this surrounding suppurative pneumonia.

Concerning the bacteriology of the necrosuppurative infections it can be said that in almost all cases culture of the pus or necrotic lung tissue revealed either *Staphylococcus aureus*, *Streptococcus hemolyticus* or one of the types of *Pneumococcus* in pure culture, mixed infections being rare. This is in contrast to anaerobic lung abscess, in which mixed infection is

universal. In one case the organism was *Micrococcus catarrhalis* in pure culture.

Necrosuppurative bronchopneumonia is, as defined before, an acute infection, with cure or fatality usually being decided in the acute phase. Infrequently the disease passes into a chronic state, with the formation of a chronic stiff-walled abscess. Bronchiectasis and chronic interstitial pneumonia may also result.

During the acute phase of the disease there may occur a spill-over infection to other parts of the lungs, or a suppurative pleuritis, in the form of a loculated or diffuse empyema or pyopneumothorax. These complications are not rare and when they do occur often alter the entire clinical picture.

The other large group of the suppurative bronchopneumonias includes those cases which present themselves with an empyema or pyopneumothorax, the underlying pulmonary lesion being a single or multiple small peripheral abscess. The pulmonary lesion is silent unless perforation with suppurative pleuritis occurs. It is probable that there are many such cases without distinctive clinical features that go on to spontaneous recovery without pleural complications and consequently go unrecognized. The pathogenesis of these cases is still obscure, the possibilities being that they are metastatic vascular or suppurative bronchopneumonic in origin.

Finally, there is the group of suppurative lesions of the lung occurring as metastatic vascular lesions during the course of a pyemia. These usually form small multiple foci in vascular segments of the lung. Larger "septic infarcts" may be found in cases of suppurative thrombophlebitis, such as in cavernous sinus thrombosis. One case occurred during the course of a scarlet fever infection with a positive blood culture for *Streptococcus hemolyticus* and a metastatic lung lesion and empyema.

Pathogenesis. In the necrosuppurative cases, the involvement of the bronchopulmonary segments and the substantial size of the lesions suggest a bronchogenic origin, with aspiration and bronchial occlusion causing the development of the lesion. However, there is as yet no direct proof for this theory. In the simple suppurative cases the problem of the pathogenesis is even more unsettled, its solution depending primarily upon the solution of the mode of origin of bronchopneumonia in general.

The pathogenesis of the metastatic vascular suppurative lesions is clear and requires no further discussion here.

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CLINICAL FEATURES, COURSE AND COMPLICATIONS OF SUPPURATIVE BRONCHOPNEUMONIA IN CHILDREN

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The clinical manifestations of suppurative bronchopneumonia are fever, cough, and, in older children, expectoration of purulent sputum. The clinical course varies considerably in its severity and may result either in early spontaneous cure or in spread to other parts of the lungs with one of three possible issues: 1) Eventual recovery; 2) chronic state with bronchiectasis; and 3) fatal outcome. The most important complications are aerobic pulmonary abscess and pleural involvement with empyema or pyopneumothorax. These complications may dominate the clinical picture and determine the final issue.

From a clinical point of view it will be advisable to classify the cases in three main groups and to note their essential features.

1. In the first group are included those cases in which the clinical manifestations, the blood picture, and even the x-ray findings do not differ in any significant way from those observed in ordinary bronchopneumonia. That this type exists has been revealed by post-mortem findings when patients died from a serious extrathoracic complication, such as otitic sepsis, occurring in the course of what was believed to be an ordinary bronchopneumonia. At necropsy the lungs showed evidence of moderately severe suppurative disease in the bronchi and pulmonary parenchyma, including numerous small pulmonary abscesses. The majority of these cases progress to spontaneous recovery, occasionally after a somewhat prolonged course characterized by slow resolution.

2. The second group is characterized by a severe and prolonged clinical course with a tendency of the disease to spread to new parts.

The fever is usually high, occasionally remittent, and may last many weeks. Exceptionally the fever curve may be remarkably low in comparison with the marked extent and severity of the process as disclosed by the roentgen film.

The cough too is of considerable severity in the majority of cases. In older children it is usually productive of purulent sputum in variable amounts.

There is nothing characteristic about the blood count except for the fact that not infrequently the leucocyte count is below 10,000 in the presence of a clinically severe pyogenic infection.

The physical signs are not unusual. Occasionally there may be a marked discrepancy between the paucity of the physical signs and the large extent of the lesion as depicted by the roentgen films.

Although the clinical course is as a rule severe, exceptionally it may be mild by comparison with the marked extent and severity of the pathological process. In many instances complete recovery takes place after a period of illness varying from several weeks to two or three months. At times recovery takes place after many months of severe illness when the prognosis appeared grave, almost hopeless, during the early acute phase of the disease. In some cases the clinical course is one of sustained severity. It is characterized by repeated spreads to new parts of the same or contralateral lung, leading to a fatal issue after a short or long period of time. In another appreciable percentage of cases complete recovery does not take place and a state of chronic bronchiectasis supervenes. Probably many of the children with chronic bronchiectasis had this type of suppurative bronchopneumonia as the underlying disease.

In this connection one sub-group deserves particular consideration. I am referring to those cases of suppurative bronchopneumonia in which atelectasis plays an important role. The pneumonic process is usually confined to one lobe and occasionally to one bronchopulmonary segment, i.e., a portion of one lobe. Early in the course of the disease the involved lobe becomes smaller in size. This may be recognized clinically by abrupt changes in the physical signs. The most significant of these signs are displacement of the mediastinal structures to the involved side and marked increase in dullness with diminished breath sounds. The roentgen examination, including lateral views, is particularly helpful in establishing the diagnosis.

The importance of this clinical subgroup lies in the fact that unless resolution is early and complete an interstitial fibrosis develops and the involved lobe remains permanently shrunken. The stage is then set for the development of bronchiectasis. The chronic pneumonitis with persistent infection will result in injury to the bronchial wall and to the pulmonary parenchyma. It will also produce marked changes in the relationship between the intra- and extra-bronchial pressure. These are the essential factors in the pathogenesis of bronchiectasis.

3. The third group comprises those cases of suppurative bronchopneumonia in which the important surgical complications dominate the picture, namely, aerobic pulmonary abscess and pleural involvement with empyema or pyoneumothorax.

In this group are included those cases in which aerobic abscess, single or multiple, is of substantial size, and the associated bronchopneumonia is relatively unimportant. In these cases surgical intervention at the optimum time may be required. In this group are not included those cases of suppurative bronchopneumonia in which numerous small areas of purulent softening takes place in the midst of the pneumonic process. These small pulmonary abscesses are too numerous to be susceptible of successful surgical drainage.

There is nothing characteristic in the clinical features of aerobic pulmonary abscess. There is no clinically recognizable phase of transition when suppurative bronchopneumonia becomes aerobic pulmonary abscess. The increasing severity of the clinical course is only suggestive. The physical signs are of little or no help. It is only with the aid of the roentgen examination that this complication can be recognized.

The advent of a severe pleural complication is usually disclosed by a dramatic change in the clinical picture with severe chest pain, marked dyspnea and great increase in toxemia as the outstanding symptoms. This is particularly true in younger infants when a tense pyothorax or pyopneumothorax develops suddenly as a result of rupture of a suppurative pulmonary focus. One would think that this complication could be diagnosed not only by the sudden change in the clinical condition of the patient but also by the physical findings which one would expect to be quite striking, namely, limited motion and prominence of the involved hemithorax, percussion hyperresonance suggesting a tense pneumothorax, flatness due to massive effusion, shifting dullness at the base and a succussion splash indicative of fluid and air, displacement of the mediastinal structures to the uninvolved side due to the massive accumulation of air or fluid. Surprisingly enough one rarely gets these classical signs of empyema or pyopneumothorax because the pleural involvement is often circumscribed. Accordingly the roentgen examination is invaluable in the diagnosis of this condition. The importance of promptly recognizing this complication is obvious since it requires immediate surgical intervention.

ROENTGEN FEATURES OF SUPPURATIVE BRONCHOPNEUMONIA

COLEMAN B. RABIN, M.D.

As may be inferred from the description of the pathology of suppurative bronchopneumonia and its complications and sequelae, the roentgen picture of this disease is a varied one. The roentgen film of the chest may depict the following:

1. Interstitial infiltrations about the bronchi, blood vessels and interlobular septa.
2. Homogeneous densities either single or multiple, of lobular, segmental, or lobar distribution.
3. Changes indicating the presence of focal, segmental, or lobar atelectasis or emphysema.
4. Multiple areas of rarefaction indicating the presence of a destructive process within the lung or bronchi.
5. Single abscess cavities of varying size.
6. Collections of fluid or of fluid and air within the pleural cavity which obscure the intrapulmonary changes.

Perhaps the most common form of the disease is the *simple* type of suppurative bronchopneumonia. In this type no evidence of a destructive lesion is seen on roentgen examination and the disease cannot be differentiated roentgenologically from other forms of bronchopneumonia. The usual form is that which shows itself on the roentgen film as an increase in the density of the pulmonary markings in one or more portions of the pulmonary field accompanied by faint interstitial infiltrations. The suppurative process in these cases is chiefly confined to the bronchial walls, and the exaggeration of the pulmonary markings and the fine streaks and occasional tiny nodules that are visible on the film represent the infiltration of the peribronchial tissue with extension into interlobular septa. In this type of the disease, local areas of atelectasis and emphysema may become manifest, producing small faint shadows demarcated within the pulmonary field by the adjacent darker hyperaerated lung. Where the areas of atelectasis are dependent upon the obstruction of very small bronchi by purulent exudate, short, horizontal or oblique shadows may be seen. These are the Fleischner's lines which one sees much more frequently in adults than in children.

At any time during the course of the disease, a larger area of pulmonary tissue, a segment, or even an entire lobe of the lung may suddenly become atelectatic. This may be manifested roentgenologically by the appearance

of a homogeneous density over the affected area accompanied by an elevation of the diaphragm on that side and a shift of the mediastinal structures to the side of the lesion. The interlobar fissures become displaced considerably, and in the case of lower lobe atelectasis the long fissure may form the hypotenuse of a rather small triangle representing collapsed lung in the cardiophrenic angle on the right side, and behind the heart on the left. Conversely, an entire lobe may become emphysematous as the result of a partial obstruction of its bronchus by exudate, and this voluminous lobe may depress the diaphragm and displace the mediastinal structures toward the opposite side.

The presence of these changes, atelectasis and emphysema, is the result of bronchial obstruction by tenacious exudate and, in conjunction with a bronchopneumonia, always suggests that the pneumonia is of a suppurative type. In the absence of these changes, the suspicion of the presence of the simple type of suppurative bronchopneumonia may be raised because of the failure of the lesion to resolve within the customary length of time. The persistence of the bronchial component of the infection may lead to a weakening of the bronchial walls sufficient to produce bronchiectasis. The bronchiectasis that occasionally results from this simple form of the disease is of the cylindrical or varicose variety, and usually can be diagnosed only after examination following the injection of iodized oil. The ordinary roentgen film shows only an exaggeration of the pulmonary markings, which may be drawn together as the result of partial atelectasis, and faint interstitial infiltrations, indicating the presence of a chronic interstitial inflammatory process.

The more severe and more destructive form of suppurative bronchopneumonia, which has been termed *necrosuppurative bronchopneumonia* (Neuhof) manifests itself roentgenologically, at the outset, by the presence of one or more irregularly defined areas of homogeneous consolidation of the lung. The shadows usually are massive and of a blotchy appearance, rather than in the form of exaggerated pulmonary markings and of fine streak-like and nodular shadows. They may be scattered throughout the lungs but are often confined to one lobe where they may coalesce to form a large area of confluent bronchopneumonia. Not infrequently a homogeneous density occurs in only one segment, to which the disease may be confined throughout its course or from which it may spread to other parts of the lung. In any case, the destructive process may manifest itself by the occurrence of one or more areas of rarefaction within the lesion, recognizable by the presence of a more or less irregular area of radio-translucency within the otherwise homogeneous shadow. Difficulty is often experienced in differentiating such areas of rarefaction due to destruction of tissue, from the areas of radio-translucency that occur during the resolution of a lobar pneumonia or simple bronchopneumonia. The sharply defined edges of the area of rarefaction within the dense shadow

of the consolidated lung and its appearance early in the disease make this differentiation possible. When a horizontal line of a level of fluid is present at the base of the rarefied area, the presence of a destructive lesion rather than of an area of resolution becomes certain.

The cavities may coalesce to form a single large one or a large single cavity may be manifest at the outset. It may or may not present a fluid

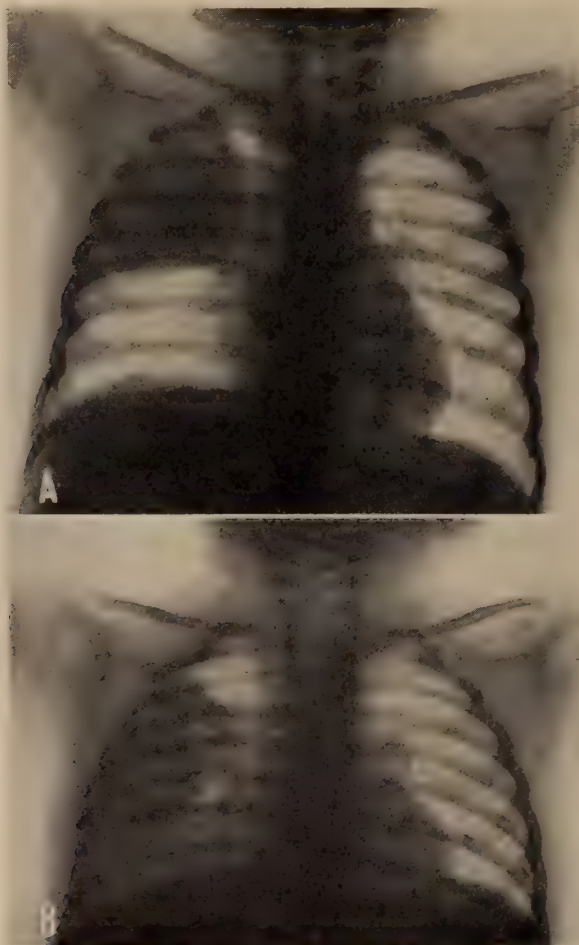


FIG. 1. A. Dense shadow of pneumonic infiltration.

B. Same case several days later with areas of rarefaction in the pneumonic zone as well as pleural invasion.

level, and although, at times, the inner wall of the cavity is smoothly outlined, it is often irregular, presenting a clover-leaf or totally irregular circumference. As the cavity develops, the infiltration of the lung often recedes, leaving the picture of a well localized cavity with a well walled-off inflammatory zone, thus constituting the picture of a true abscess cavity. (The appearance of such a cavity without any fluid within it is

in sharp contra-distinction to the cavity that occurs in putrid abscess of the lung which practically always shows a fluid level at the stage when the aerated cavity can be seen roentgenologically). These cavities, particularly those that are devoid of exudate within them, may rapidly become small and disappear within a very short time, possibly because of closure

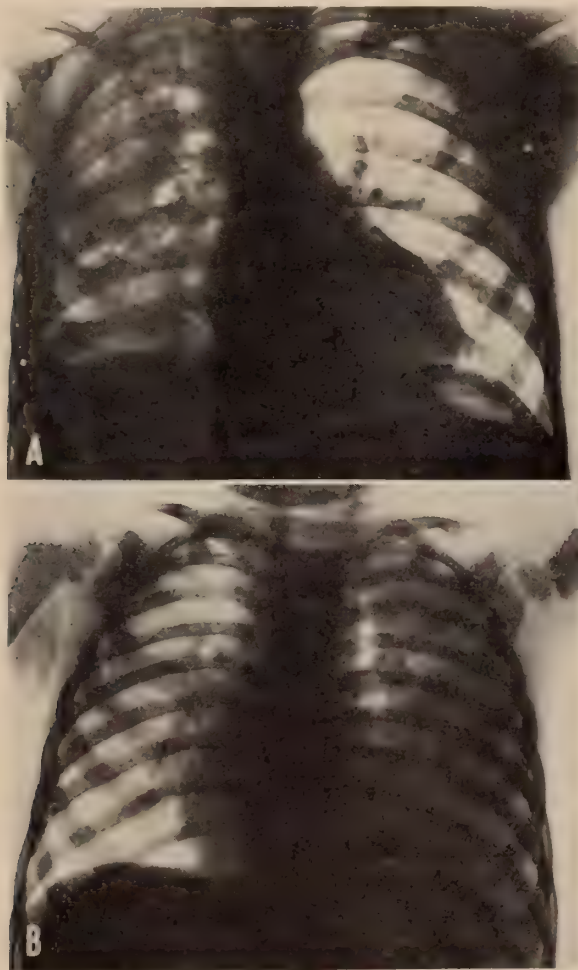


FIG. 2. A. Widespread areas of necrosuppurative bronchopneumonia with multiple fluid levels.

B. Unsuspected areas of pulmonary destruction in the midst of a pneumonic process with pleural extension.

of the bronchus leading into them, and conversely they may increase rapidly in size in spite of the fact that the surrounding infiltration absorbs. Simultaneous with the increase in the size of the cavity, its walls, which previously appeared irregular may become perfectly smooth and round. An explanation for this course of events is to be found in the as-

sumption of a valve-like mechanism formed by exudate partially occluding the bronchus entering the cavity.

In rare instances, particularly in the case of the larger "balloon" cavities, the cavity within the lung may persist indefinitely in spite of the complete or almost complete elimination of the infection. The persistent cavity appears roentgenologically as a thin circular or oval annular shadow which can be filled with iodized oil and thus demonstrated to be a real cavity within the lung. Such lesions are often called air cysts and have often been considered as congenital lesions, particularly in those cases in which the initial infection occurred during infancy and which the patient cannot recall.

Either the single abscess cavity or the smaller areas of suppuration may be complicated by a pleural effusion or a pyopneumothorax which ob-



FIG. 3. Pulmonary abscess of the middle lobe in a preexisting area of necro-suppurative bronchopneumonia. Sympathetic pleural effusion.

scures the further course of the disease in the underlying lung. When the effusion is not large enough to produce a complete collapse of the lung; the shadows in the lung may be sufficiently characteristic to permit recognition of the underlying cause of the pleural infection.

In those cases in which multiple small areas of suppuration occur within the lung parenchyma, sacculated bronchiectases may appear and remain permanently, albeit in some cases the infection may have subsided and the patient become symptom-free. In a large percentage of these cases of sacculated bronchiectasis, either moist or dry, the affected lobe is atelectatic. The atelectasis, in these cases, occurs in the acute stage of the disease and presumably is caused at that time by bronchial obstruction. The affected lung remains collapsed permanently either because its lung tissue has been destroyed, or because the fibrous tissue deposited during the course of organization of the exudate has prevented reëxpansion.

TREATMENT OF ACUTE SUPPURATIVE BRONCHOPNEUMONIA IN CHILDREN

GEORGE J. GINANDES, M.D.

Although acute suppurative bronchopneumonia may be divided into three convenient clinical groups, no sharp lines of demarcation can actually be drawn. The treatment of the first two groups is essentially medical. The cases differ from each other mainly in the severity of the process. *Group 1* is the mildest group. It comprises those cases which resemble an ordinary bronchopneumonia, and the treatment is essentially the same. Comment will, therefore, be restricted to the more important therapeutic measures.

Specific Therapy. This includes chemotherapy and serum therapy. Our experience with chemotherapy and that reported in the literature have shown that the sulfonamid drugs have a broad range of usefulness and a wide margin of safety. The selective effectiveness of these drugs, their dosage and the modes of administration are well known.

We have been using .2 gram per kilogram of body weight in divided doses over a period of 24 hours when administering sulfanilamide and sulfapyridine. Sulfathiazole has been used in doses up to .4 gram per kilogram. These doses give a satisfactory concentration in the blood.

The period of administration is determined by the effect. If resolution is progressing and the temperature is down, the drug is discontinued after a few days. If resolution has not occurred, but the toxic symptoms and the clinical condition seems to be favorably influenced by the drug, it is continued. This may be a matter of a few days or even weeks. When the progress of the disease is unaffected and the patient fails to respond to one drug, another derivative is tried. This is especially important if reculture demonstrates a change in the predominating organism.

The importance of bacteriologic studies in the light of this newer therapy cannot be overemphasized. Cultures of the sputum and the blood, and typing should be performed whenever possible before the drugs are administered, since their use makes the isolation of the organism increasingly difficult. Needless to say, the patient should be closely watched for toxic symptoms due to the drug. These symptoms are now well known.

Although the number of cases in our series treated with the sulfonamid drugs is as yet too small to permit us to draw conclusions, our experience has been encouraging and we believe that selective chemotherapy should be vigorously tried in all cases of acute suppurative bronchopneumonia.

As for serum therapy, we have had little experience with the use of specific serum. We have used serum, when available, in cases where chemotherapy failed to influence a persistently positive blood culture or

where contraindications to chemotherapy were present or developed, such as renal damage, severe anemia, agranulocytosis or other symptoms of drug toxicity. From the experience of others, it would appear reasonable to try combined treatment with serum and chemotherapy in debilitated patients or in severe cases with bacteremia.

Supportive Measures. These are no less important than specific measures. Rest, the judicious use of sedatives and stimulants, relief of abdominal distension, and the maintenance of adequate tissue hydration by parenteral route if necessary, need only be mentioned.

Transfusion as a form of therapy should be stressed. When the disease is severe, the child toxic or anemic or when nutrition is depleted, repeated small transfusions of whole blood or plasma have been especially helpful. When the red cell count and hemoglobin are high, a plasma transfusion may be of aid in replacing protein and maintaining circulatory volume. Transfusions have been of particular value in offsetting the hemolytic and anti-regenerative influence of the sulfonamid drugs on the blood-forming organs. We have not infrequently been impressed by a sudden drop in temperature and an improvement in the general condition of a patient following a small transfusion. The amount of blood given in a single transfusion may vary from 50 to 75 cc. in an infant and from 200 to 250 cc. in an older child. Here, as in the case of parenteral fluids, the rate of administration must be slow and the drip method is preferable.

The *early* use of oxygen should be emphasized. When cyanosis appears, when respiration is labored or unduly rapid, or when the circulation is embarrassed, oxygen is of paramount value. We rely on the oxygen tent as a mainstay in the treatment of these cases and we use it early and freely. Where the sulfonamid drugs obscure the interpretation of the cyanosis, we give the patient the benefit of the doubt and use oxygen.

The majority of the cases in the first group go on to complete resolution after a period of convalescence which is usually longer than in the ordinary bronchopneumonia. This process may extend over weeks or even months in severe cases. It is important to maintain an adequate nutrition, including a high vitamin intake, throughout the period of convalescence. A change to a less rigorous climate, when convalescence is slow, often facilitates recovery.

In the *second group* are included the severe cases which are apt to run a violent and prolonged course, with a tendency to a spread of the disease to new parts. The treatment of this group is identical with that just described, but the severity of these cases demands more vigorous and more persistent use of all the available measures. In addition, there are a few procedures which should be mentioned in connection with these severe cases.

Pneumothorax. The use of pneumothorax therapy in certain selected cases of atelectatic bronchopneumonia is worth noting. Pneumothorax therapy may nullify an otherwise compromising shift of the mediastinum.

It may facilitate resolution of a persistent pneumonitis and neutralize the effect of an increasing negative pressure on damaged bronchi and lung tissue, thus possibly preventing the development of bronchiectasis and fibrosis.

Bronchoscopy. This is of value for differential diagnosis and for the removal of a suspected foreign body. We reserve bronchoscopy for these indications and do not use it routinely in treatment.

Despite all these measures, the outlook in the group of severe suppurative bronchopneumonia is problematic. Some of the children fail to respond and die of a diffuse pneumonitis with multiple lung abscesses. A number of them develop chronic bronchitis and bronchiectasis and are subject to recurrent attacks of bronchopneumonia. Still others have a persistent chronic pneumonitis and fibrosis. A certain percentage of this group, however, despite a long stormy course lasting weeks or even months, will go on to complete resolution without apparent residual symptoms.

Whereas the management of the first two groups described is essentially medical, treatment of the *third group* is essentially surgical. This group includes the cases that develop lung abscesses or pleural complications.

In those cases that develop single or multiple lung abscesses, the underlying pneumonic process also requires medical treatment. However, timely surgical intervention may avert the extension of the process as well as serious pleural complications. One thing that should be emphasized is the fortunate tendency for spontaneous resolution of aerobic lung abscesses in children. This has been brought strikingly home to us in the past few years, when we have seen several such cases weather a serious course and accomplish extraordinary repair of multiple lung abscesses.

The pleural complications that may appear in the course of a suppurative bronchopneumonia may occur suddenly or may develop insidiously, and must be constantly watched for. When the onset is acute and a tense empyema or pyopneumothorax develops, the indications for surgical drainage are urgent. Where the onset is more insidious and less dramatic, adequate and prompt surgery is no less important. Although the medical management of the underlying suppurative bronchopneumonia must not be neglected, the proper and timely surgical treatment of empyema and pyopneumothorax may result in complete cure. To accomplish this, early and close collaboration between the pediatrician and the surgeon is of paramount importance. Unnecessary temporizing, repeated Potain aspirations and syringe drainage, although occasionally successful, may be responsible for loculation and the development of chronic empyema.

In conclusion, in the management of all the varieties of suppurative bronchopneumonia, the importance of specific and supportive measures must be emphasized. It should be remembered, however, that those phases of the disease that are dominated by complications are essentially surgical problems and must be treated as such.

THE TREATMENT OF AEROBIC PULMONARY ABSCESS

ARTHUR S. W. TOUROFF, M.D.

Aerobic (non-putrid) pulmonary abscess, a not infrequent complication of necrosuppurative bronchopneumonia, occurs essentially in two forms, i.e., "interstitial" and "segmental." "Interstitial" abscesses usually present as multiple lesions of small size (about $\frac{1}{4}$ of an inch or less in diameter) scattered throughout the area of pre-existing necrosuppurative bronchopneumonia. Their presence ordinarily does not result in clinical or therapeutic features which differ from those of the antecedent pneumonic process. If such a lesion should perforate into the pleura, however, the clinical manifestations and treatment become those of the resulting pleural infection. By contrast, "segmental" abscess is most often a solitary lesion of substantial size (1 to 4 inches in diameter) which usually occupies much or all of a broncho-pulmonary segment. Henceforth, our discussion shall be confined solely to abscesses of this type.

The conversion of an area of necrosuppurative bronchopneumonia into an aerobic "segmental" pulmonary abscess, may take place slowly or rapidly. Furthermore, the process of cavitation may involve little, or almost all, of the area of pre-existing necrosuppurative bronchopneumonia. Thus, there may be no clearly definable dividing line, either pathologically or clinically, between the termination of necrosuppurative bronchopneumonia and the beginning of pulmonary abscess, for the two may, and often do, co-exist.

The treatment of aerobic "segmental" pulmonary abscess may be either medical or surgical depending upon the precise nature of the lesion in question. The non-surgical treatment is precisely the same as that of the antecedent or coexisting pneumonic process and, therefore, will not be described. It should be mentioned in passing that we have not found postural or bronchoscopic drainage of definite value and do not employ them. The indications for operative treatment in cases of aerobic pulmonary abscess are less precise and clean-cut than in cases of anaerobic (putrid) abscess. The reasons for this are obvious if one recalls that a putrid abscess is a well-encapsulated lesion while an aerobic abscess not infrequently consists of a collection of pus in the midst of an extensive area of necrosuppurative bronchopneumonia. Thus, prompt cessation of symptoms is the rule following evacuation of anaerobic abscess while little amelioration of symptoms may be noted following operation in certain cases of aerobic abscess. Another reason for difficulty in formulating operative indications in cases of aerobic abscess is the great tendency

toward spontaneous recession of even large lesions. Therefore, a more conservative attitude toward operative treatment exists in cases of aerobic as compared with anaerobic abscess.

For purposes of surgical consideration, cases of aerobic abscess may be divided into three main types as follows: 1) Pulmonary excavation in the midst of, and merely an incidental part of, an extensive area of necro-suppurative bronchopneumonia; 2) pulmonary excavation as a predominant lesion, but surrounded by a considerable area of necrosuppurative bronchopneumonia; and 3) "typical" pulmonary abscess in which the excavation is surrounded by only a narrow, sharply-limited zone of pulmonary infiltration. Necrosuppurative bronchopneumonia may involve several areas of the lung and even the opposite lung, concomitantly or in sequence. Since each of these areas may undergo cavitation, multiple "segmental" abscesses of the three types previously described may be present in any combination. While each case must be considered individually, certain general rules apply in the selection of therapy. These may be summarized as follows: 1) In cases in which a pulmonary excavation, whether large or small, lies in the midst of an extensive area of necro-suppurative bronchopneumonia, the treatment in general is non-surgical; 2) in cases in which multiple lesions are present, the treatment in general also is non-surgical; 3) in cases in which "typical" pulmonary abscess surrounded by a narrow zone of pulmonary infiltration is present the treatment *may be* surgical.

In "typical" cases of aerobic pulmonary abscess, the collection of pus is essentially monolocular although at times the cavity may contain recesses. Because of the fact that a broncho-pulmonary segment is involved, the peripheral portion of the abscess cavity usually is situated quite superficially beneath the surface of the lung (at a depth usually not exceeding $\frac{1}{4}$ of an inch or $\frac{3}{8}$ of an inch). The shell of lung overlying the lesion in this area is compressed and avascular, and is united to the parietal pleura by dense adhesions. The cavity may be filled with pus and air in varying amounts depending on the degree of spontaneous drainage taking place by way of the communicating bronchus or bronchi. The foregoing characteristics make such lesions amenable to surgical treatment and give reasonable assurance that if operation is carried out properly, a satisfactory result may be anticipated. Because of the fact that a certain proportion of such lesions may subside spontaneously, however, operation is not recommended in all cases but is reserved for those in which the clinical course is severe or those in which the lesion is enlarging or remains stationary over a period of several weeks. There are two other operative indications which we recognize in cases of aerobic abscess. These are: 1) Impending perforation of the lesion into the pleura as indicated by the clinical course and roentgen examination; and 2) actual perforation of the lesion into the pleura with the development of intra-pleural suppuration.

The operation which we employ in cases of unperforated abscess consists of a one-stage procedure in which the abscess cavity is evacuated, unroofed and packed through the zone of limiting visceroparietal adhesions. In order to perform such a procedure with safety, the operative incision must be accurately placed at a site determined by careful pre-operative studies in localization. Only a short segment of one or occasionally two

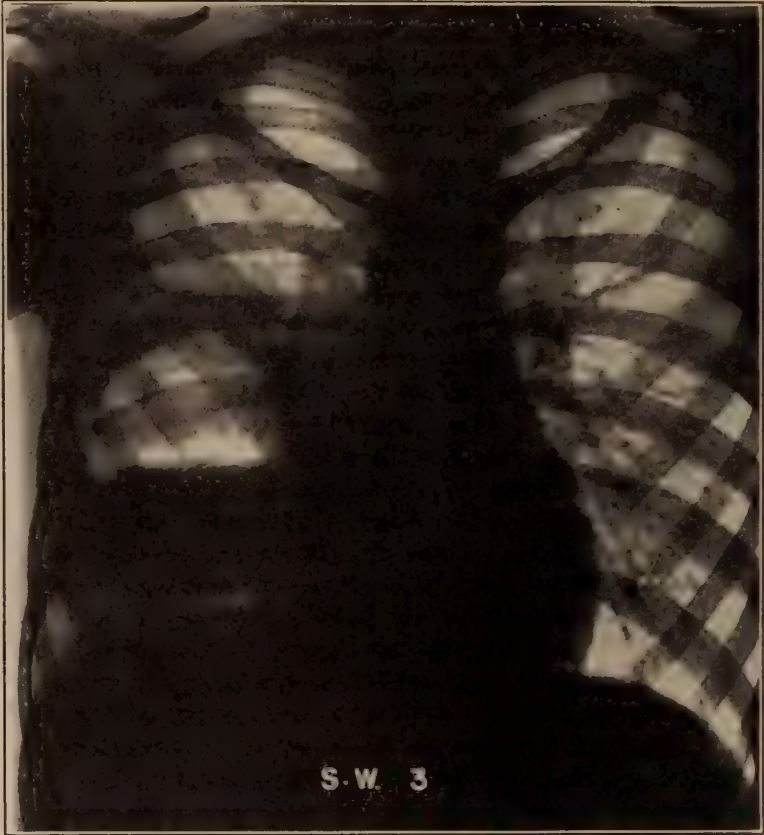


FIG. 1. "Typical" non-putrid abscess of right lower lobe. Note large size of lesion and minimal surrounding pulmonary infiltration. Lesions of this type are potentially surgical.

ribs is removed, usually under local anaesthesia. The underlying visceroparietal adhesions are identified and pus located superficially within the lung with the aspirating needle. The lesion then is entered, evacuated and unroofed by partially excising the overlying lid of pulmonary tissue. After all the pus and detritus have been removed and the interior of the cavity inspected, the latter and the superficial wound are packed with gauze. Postoperative care is relatively simple and consists of repacking the cavity lightly, at intervals of every three to four days until the latter

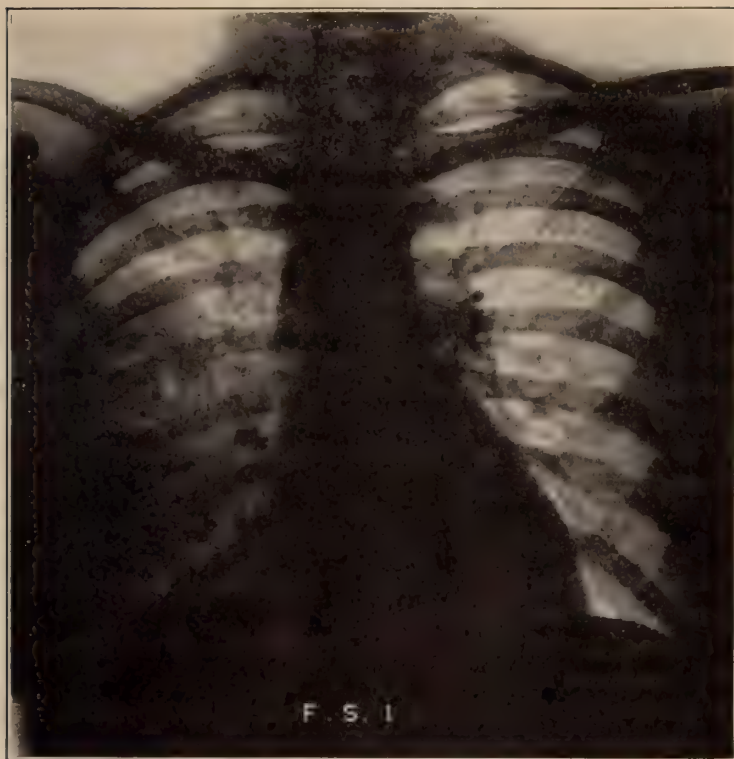


FIG. 2. Non-putrid abscess of right lower lobe. Note extensive area of pulmonary infiltration (necrosuppurative bronchopneumonia) containing several small fluid levels. Lesions of this type are non-surgical.

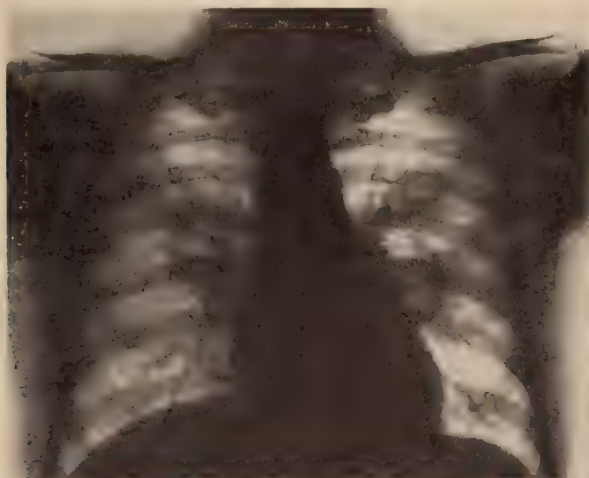


FIG. 3. Multiple bilateral non-putrid abscesses. Lesions of this type are non-surgical.

is obliterated and the bronchial fistulae closed. In certain instances in which the cavity is unusually large it may become reduced in size but then show no further tendency to become obliterated. In such cases some type of plastic closure usually is necessary, and we have found free transplants of fat to be of particular value in effecting satisfactory obliteration.

Since pulmonary abscess complicated by perforation into the pleura is beyond the scope of this presentation, this subject will not be discussed in detail. Attention should be called, however, to the fact that at times it may be impossible to distinguish clinically and roentgenographically between a large unperforated pulmonary abscess and an encapsulated pyopneumothorax. Under such circumstances, the patient is apt to be operated upon, because the lesion is assumed to be a pyopneumothorax. However, it may prove, at operation, to be an unperforated abscess confined entirely to the pulmonary substance and for this reason such lesions must be approached with care lest the pleura be accidentally opened and contaminated.

SUMMARY

Our experience with the treatment of unperforated aerobic pulmonary abscess may be summarized as follows:

- 1) All cases of typical abscess which were sufficiently mild not to warrant operative treatment recovered.
- 2) All cases of typical acute abscess subjected to operation recovered and have remained well for periods of from one to eight years.
- 3) Operation in cases of pulmonary excavation surrounded by considerable area of necrosuppurative bronchopneumonia has not had a favorable effect upon the latter, and at times appeared to induce spread of infection, which ended fatally.

THE PLEURAL COMPLICATIONS OF ACUTE SUPPURATIVE AND NECROSUPPURATIVE BRONCHOPNEUMONIA

HAROLD NEUHOF, M.D.

Because of pleural invasion, an indication for surgical treatment may arise suddenly or gradually, early or late in the course of suppurative or necrosuppurative bronchopneumonia. Thus, one may be forced to face the problem of management of a severe pleural infection during the course of a bronchopneumonia. The contrast between this situation and that of empyema complicating ordinary pneumonic lesions is obvious. Not only may the problem be one of relieving pleural infection in the presence of acute suppurative bronchopneumonia, but frequently there is also the problem of relieving mechanical respiratory and cardiac embarrassment. Indeed, relief of the latter is sometimes more important and urgent than elimination of the pleural infection.

In contrast to the ordinary pneumonias, the pleural complication of the suppurative bronchopneumonias is characterized by the existence of a perforation of the pulmonary focus. Since necrosis of the wall of a bronchus of varying size is an essential feature of the pathology of necrosuppurative bronchopneumonia, a communication between an open bronchus and the infected pleural space can be anticipated. The evidence of a bronchial opening is demonstrable radiologically, at operation or after operation, in most instances. The reason for the inability to demonstrate the existence of a perforative lesion, in a small proportion of cases, probably lies in the fact that the focus occasionally is small (rupture of a so-called cortical pulmonary abscess) or collapses and then is obliterated after rupture.

A useful clinical classification of the pleural infections has been found to be in two groups:

1. Localized empyema or pyopneumothorax. There usually is a large perforation of a substantial pulmonary focus. The mediastinum is not displaced in most instances. Air (and consequently fluid level) is present in the preponderance of cases. Its absence can be ascribed to blockage by purulent exudate of one or more bronchial orifices in the wall of the pulmonary abscess or to collapse and occlusion of the abscess cavity.

2. Diffuse empyema or pyopneumothorax. The pulmonary perforation usually is small and insignificant. The mediastinum is displaced almost invariably.

As already indicated, a segmental pulmonary abscess, which always is of substantial proportions, is to be regarded as the common cause of localized pleural infections (the first group). Walling-off adhesions, de-

rived chiefly from the surface of the pulmonary focus, tend to localize sharply the empyema or pyopneumothorax. As a result the symptoms of pleural invasion usually are more insidious than in the second group (the diffuse infections). Because of its relatively large size, the symptoms

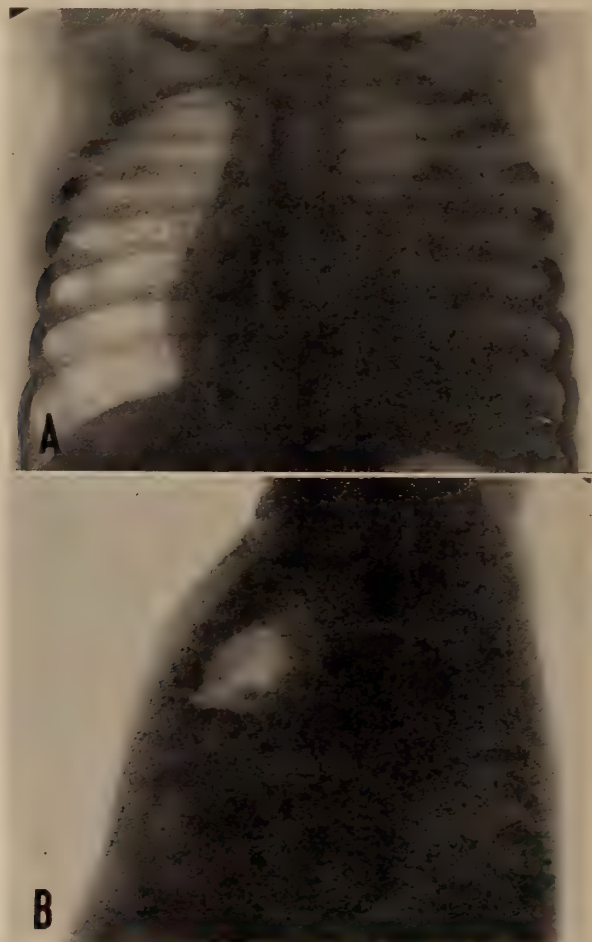


FIG. 1. A. Localized tension pyopneumothorax in an infant. Note dislocation of mediastinum.

B. Lateral view, same case. The anterior encapsulation made anterior drainage imperative.

and roentgenographic evidence of the causative pulmonary abscess may persist after a small perforation into the pleura has occurred. The empyema or pyopneumothorax may be of small size or may be situated in relatively inaccessible regions such as the depths of interlobar fissures. The roentgenological features of pyopneumothorax are often, but by no means always distinctive. The differentiation between a pyopneumo-

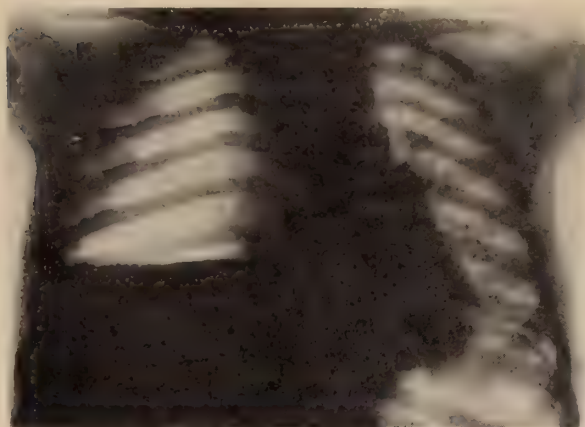


FIG. 2. Total extreme tension pyopneumothorax due to large perforative pulmonary lesion.



FIG. 3. Lateral view of multilocular encapsulated pyopneumothorax. Pronounced destruction of the pulmonary parenchyma was found at operation.

thorax and an unperforated pulmonary abscess may be difficult or even impossible. Emphasis should be placed on the necessity for precise roentgenological localization of the pleural infections under discussion in order to render safe the operative entry of a small encapsulated empyema or of an empyema in an atypical situation. In such cases, exploratory aspiration should be performed only if operation can be proceeded with immediately. Since operation rarely is urgent in cases of encapsulated pleural lesions, all the necessary studies in advance of operation can and should be carried out with careful deliberation. Three features of the



FIG. 4. Lateral view of pulmonary abscess on the verge of perforation into the interlobar fissure. The differentiation from pyopneumothorax is virtually impossible.

operative treatment we advocate may be stated here. Drainage of the pleural collection of pus should be established by means of a fully adequate opening. Special attention should be given to encapsulations which are often situated in recesses. The orifice of a perforated pulmonary abscess should be enlarged if found at operation to be too small for adequate drainage of the pulmonary focus.

Concerning the second group, in which the pulmonary perforation usually is insignificant or may not be demonstrable, an underlying segmental bronchopneumonia appears to be rare. The existence of smaller suppurative or necrosuppurative foci, not necessarily of bronchopneumonic nature (lymph-angitic? vascular? metastatic?) must be postulated in the pre-

ponderance of instances of diffuse pleural infections. Since the lesions usually are smaller or more ill-defined than in the first group, limiting pleural adhesions derived from them are rarely effective in confining the pleural infection. Thus, although the empyema or pyopneumothorax does evolve gradually in some cases, the onset often is abrupt, the evolution of the empyema or pyopneumothorax rapid, and the clinical course severe. A fully developed and ominous picture may already be seen early in the course of the pulmonary infection. I wish to place emphasis on the surgical management of these severe cases, for, in contrast to well-encapsulated pleural lesions, the outcome may be dependent on timely and correct treatment. As a rule closed drainage should be the primary procedure because of the virtual absence of pleural adhesions and, consequently, of mediastinal fixation. The point to be made is that early closed drainage may be imperative, even during the course of a pneumonia, in order to relieve dislocation of the heart and mediastinum or/and severe toxemia derived from rapidly increasing pus in the pleural space. The arguments which have been set forth elsewhere¹ against Potain treatment, aspiration and air replacement, and other temporizing methods in the management of pleural infections, apply with particular force to the severe cases in question. Closed drainage alone rarely suffices. A secondary open operation often is required after an emergency closed drainage in order to provide drainage of residual pleural suppurative foci, drainage of an underlying pulmonary abscess, or, at times, in order to close a large bronchopleural communication. The prognosis in these cases of severe pleural infection, most frequently seen in infants and young children, depends in part on whether the underlying suppurative pulmonary focus is extensive or limited, single or multiple, on whether the infection of lung and pleura is fulminating or is less severe, and on the speed of evolution of the infection. The prognosis also depends in part on well timed and logically conceived surgical intervention. Tricky procedures which do not bear critical analysis can and do lead to occasional or even to unexpected recoveries, but consistent worthwhile results can be anticipated only upon the application of well conceived surgical measures.

¹ Neuhof, H. and Hirshfeld, S.: Suppurative Pleuritis in Children. Its Pathogenesis, Diagnosis and Treatment. *Am. J. Dis. Child.*, 44: 973-993, 1932.

CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Wednesday, November 15, 1939

Scurvy due to Prolonged Sippy Diet or Purpura due to Skeletal Metastases from Primary Gastric Carcinoma of Five Years Duration

[From the Medical Service of Dr. George Baehr]

History (Adm. 441156; P.M. 11187). A forty-nine year old peddler was admitted to the hospital for the first time in 1934, complaining of epigastric discomfort and eructations of ten years duration. This had always been relieved by alkalis. In 1933, one year before admission, he noted weakness and epigastric pain radiating to the back, which was not relieved by eating. He was relieved for six months by an ulcer diet, but he then became worse. He began to lose weight, vomited frequently and had several tarry stools.

Examination. The patient was a pale, chronically ill man. The liver was felt two fingers below the costal margin. There was no abdominal tenderness. The clinical impression was duodenal ulcer.

Laboratory Data. Hemoglobin, 45 per cent (Sahli). White blood cells, 7,500 with a normal differential count. The urine was negative. On one occasion the stool was strongly guaiac positive. On a fasting stomach there was a residue of 10 ounces. The blood chemistry findings were normal. The Rehfuß test meal showed a maximum total acidity of 66. Barium studies of the gastro-intestinal tract showed a pyloric obstruction with 80 per cent gastric residue after six hours. There was an irregular constriction in the prepyloric region suggestive of a malignancy.

Course. A posterior gastro-enterostomy was performed after preliminary supportive treatment. At operation a large inflammatory tumor mass was found in the region of the pylorus adherent to the liver. The patient was discharged with his wound well healed, and feeling well. He was well for two years and then for six months had dull pain in the middle of his back following meals. He had one tarry stool during this period. He was re-admitted to the hospital for investigation.

Second Admission. A Rehfuß test meal was again performed and showed free acid still present in the stomach, with a maximum total acidity of 32. X-ray studies revealed a penetrating gastric ulcer on the lesser curvature of the stomach opposite the gastro-enterostomy stoma. The possibility of malignancy in this case was considered, but in view of the poor condition of the patient, and the extensive operation necessary, it was deemed safer to continue conservative therapy under close observation. He was followed in the clinic, with the persistence of symptoms. Two gastroscopies were done. The pylorus was visualized. Two black silk sutures were seen imbedded in the mucosa. On the anterior wall converging rugae, red and congested were seen, and at the apex of the convergence a small, apparently healed ulcer was noted.

Third Admission. The patient was admitted to the hospital for the last time on May 29, 1939. Four weeks prior to admission he developed frequent epistaxes which continued daily for over two weeks. Three days prior to admission persistent gross hematuria appeared. At the same time he developed dizzy spells, severe frontal and occipital headache, mental confusion, mumbling and inarticulate speech, and weakness of the right arm and leg. For three days prior to admission he had severe bilateral sharp lumbar pain.

Examination. Examination at this time revealed an obese male. The blood pressure, which several years ago had been 130 systolic and 80 diastolic, had risen under observation to 170 systolic and 110 diastolic. The patient was severely aphasic. The right extremities were weak, with increased deep reflexes.

Laboratory Data. Hemoglobin, 96 per cent (Sahli). White blood count, 14,700 with a normal differential count. There were 160,000 platelets per cubic millimeter. The bleeding time was 3 minutes and the clotting time was 6 hours. The tourniquet test was slightly positive. Sternal marrow aspiration was normal. The urine was loaded with red blood cells and had a trace of albumin. Blood was found in the stool and 900 fresh red blood cells per cubic millimeter were found in the cerebrospinal fluid. Electrocardiogram showed changes suggestive of a posterior wall infarction. Intravenous pyelogram was negative.

Course. After one week in the hospital the patient suddenly went into coma, breathed stertorously for a few minutes, and died.

Necropsy Findings. *Dr. Klemperer.* A scirrhus carcinoma, arising just opposite the gastro-enterostomy stoma was found. The stomach wall was diffusely invaded, and fibrotic strands of carcinoma were seen running through the muscularis. Many lymph nodes were involved, the retro-peritoneal and posterior mediastinal nodes being especially enlarged. The lungs, which appeared normal grossly, had microscopic tumor emboli in the small arteries. The heart revealed hypertrophy and a terminal thromboendocarditis. Emboli from this had caused infarcts in the kidneys and myocardium. The bone marrow was diffusely involved in an osteoplastic carcinomatosis. We have had a few cases in the past of gastric carcinoma with bone marrow metastasis and purpura.

Comment. *Dr. Bachr:* The terminal clinical picture of purpura, epistaxes for five weeks, gross hematuria, finally cerebral hemorrhage, is explained by the pathologist as due to the bone marrow metastases of carcinoma. I should like to point out, however, that the blood platelets throughout the course of the disease, were never low enough to cause purpura. At no time was there any evidence of an aplastic blood picture. I cannot, therefore, accept the bone marrow metastases as an adequate explanation for the purpura. It must be remembered that for fifteen years this man was on a limited diet and for six years he had been on a Sippy diet which is notoriously deficient in vitamin C. A vitamin C deficiency may, therefore, explain the bleeding tendency in this case. It must be admitted that the type of bleeding is not entirely typical of scurvy. Yet it should be remembered that the patient was also suffering from a wasting disease, a gastric carcinoma probably of five years duration and this could have modified and accentuated the symptoms of scurvy.

Reported by *Abner Kurtin, M.D.*

Toxic Cirrhosis of Liver

[From the Medical Service of Dr. B. S. Oppenheimer]

History (Adm. 443202; P.M. 11236). This was the first admission of a thirty-nine year old white married woman with the chief complaint of jaundice. Her past history included a twelve year period of intermittent epigastric pain which began eighteen years before admission following a miscarriage and continued for six years. Two years before admission the patient noted the onset of painless icterus, accompanied by dark-colored urine, light stools, itching, and diarrhea. There were no chills or fever. She had also had occasional epistaxis and bleeding from the gums. At another hospital an exploratory operation was performed. The patient was informed that she had cirrhosis of the liver and that a Talma procedure had been performed. She left the hospital unimproved. Icterus persisted and the itching has been partially controlled by injections of calcium. Eight months before admission there was a severe uterine hemorrhage, accompanied by a drop in hemoglobin to 45 per cent; the hemorrhage required packing several times. For the month before admission she had been receiving vitamin K with some improvement in the hemorrhagic tendency. During the few months before admission she had occasional abdominal distention with pain in the right lower quadrant of the abdomen. The jaundice is believed to have fluctuated in intensity during the two years before admission. Three weeks before admission she developed a cough and fever. A right thoracentesis greatly relieved the cough. An abdominal tap was unproductive of fluid.

Examination. The patient was well developed, fairly well nourished, and markedly icteric. The sclerae were icteric. The pupils were slightly irregular, but reacted well. The tongue was beefy red with smooth margins. The pharynx was injected and velvety in appearance. The lungs showed evidence of fluid at the right base. In the left chest there were moist and inconstant râles. The heart showed a rough systolic murmur at the apex. The second pulmonic sound was reduplicated. The blood pressure was 100 systolic and 40 diastolic. The abdomen was soft. There was a well healed right pararectus scar. The liver was palpable four fingers below the costal margin, it was firm and non-tender. Just along the angle between the lower border of the liver and the right border of the rectum, a round, tense, smooth tender mass could be felt. The spleen was palpable three fingers below the costal margin. Shifting dullness was present in the flanks. Dilated veins were visible and a *caput medusae* was present about the umbilicus. The skin was markedly icteric, covered with numerous ecchymoses. Numerous scratch marks were present. A papular, lichenified eruption was present over the hands. There was clubbing of the fingers and toes. Pitting edema was present over the legs and sacrum. Neurological examination was negative. Rectal examination was negative, except for one occasional hemorrhoidal tab.

Laboratory Data. Hemoglobin, 82 per cent; white blood cells, 9,900 with a normal differential count. The stool was tan, guaiac negative, and urobilin positive. The urine showed a faint trace of albumin, 3 plus bile and urobilin present up to a 1:10 dilution. The tourniquet test was negative. Bleeding time, 2 minutes and 45 sec-

onds; coagulation time, 7 minutes; clot retraction time, 30 minutes. Prothrombin time was normal. The fragility test showed increased resistance of the red blood cells. Sedimentation time was normal. Galactose tolerance test showed an excretion of 0.7 grams. Icterus index, 35; blood cholesterol, 190; ester, 40 mg. per cent; bilirubin, 5; van den Bergh, direct positive; phosphorus, 6; calcium, 8 mg. per cent; urea nitrogen, 7 mg. per cent; total protein, 5.1 per cent; albumin, 3.2 per cent; globulin, 1.9 per cent. The Takata-Ara reaction was negative. The blood Wassermann reaction was negative. The venous pressure and saccharin time were normal. A blood vitamin C test revealed high normal saturation. Fluid, obtained on pleural aspiration, failed to show any tumor cells. X-ray examination of the abdomen revealed four small ring-shaped concretions in the right upper quadrant, probably gall stones. X-ray examination of the chest showed a right pleural effusion.

Course. The patient continued to run a low-grade fever. Daily injections of calcium gluconate were given to control the pruritus. She was treated with a high carbohydrate low fat diet with the addition of vitamin B, C, K, and viosterol. Although there was unanimity of opinion that this might be a biliary cirrhosis was considered. This was based on the presence of a palpable gall bladder and the x-ray evidence of biliary calculi, which suggested a possible common duct obstruction of varying degree. Fully cognizant of the dangers operation was, therefore, attempted. A right upper quadrant incision was made but because of marked bleeding encountered from large cavernous-like veins it was impossible to proceed beyond incision of the subcutaneous tissue and the wound was closed. Five days postoperatively, the patient suddenly became unresponsive. The reflexes were normal, with equivocal bilateral Babinski signs. There was slight oozing from the left nostril and bilateral subconjunctival hemorrhages. The temperature rose sharply reaching 107°F. within twenty-four hours and the patient died. At the time of death, the blood urea nitrogen was 7 mg.; icterus index, 30; cholesterol, 220 mg.; esters, 45 mg. per cent.

Necropsy Findings. The liver weighed 1800 grams, i.e., it was not atrophic. It was nodular, but coarsely so. There were no calculi in the common duct, nor were there stasis or dilatation in any portion of the biliary tree. The gall bladder was not enlarged, but did contain four stones. The mass, palpable clinically, consisted of fascia and omentum attached to the under surface of the liver as a result of the previous Talma omentopexy. The spleen was enlarged. The splenic vein was dilated and there was evidence of considerable collateral circulation.

Comment. Dr. Klemperer: The picture of the liver here is that seen in coarse nodular cirrhosis which is the end-result of a severe liver degeneration. It is different, pathologically, from Laennec's cirrhosis. It is definitely not a biliary cirrhosis as shown by the absence of any changes in the biliary tree. It may well be called a toxic cirrhosis, and it is in this group that icterus is an early and prominent feature.

Dr. Baehr: An interesting clinical feature is the presence of clubbing. This is not infrequently seen in cases of long standing jaundice. Of further interest is the negative Takata-Ara reaction, in spite of the marked and prolonged liver cirrhosis.

Reported by Max Ellenberg, M.D.

CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D., *presiding*

Monday, March 25, 1940

Case 7.¹ Neurospongioblastoma, Right Cerebral Hemisphere

[From the Neurological Service of Dr. I. S. Wechsler and the Neuro-Surgical Service of Dr. I. Cohen]

History (Adm. 446359; P.M. 11286). A woman, 56 years of age, was admitted to the hospital on September 26, 1939, complaining of diffuse headache of seven weeks duration. One or two days after the onset she began to experience visual hallucinations, such as a parrot looking into her window, ponies in the street, and people looking into her home from the "elevated" tracks. Two days before admission she became drowsy, and developed weakness of the left arm and leg, associated with fine tremors of the leg.

Examination. The patient was in semi-stupor. Her right upper extremity displayed grasping movements and she would pick aimlessly at the nose and bedclothes. When aroused, she was confused and apathetic, confabulated and had a marked memory defect.

Neurological Status. Right-sided skull tenderness was present. There was marked bilateral papilledema with exudate and hemorrhages, more marked in the left eye. The left pupil was larger than the right but pupillary reactions were normal. The left palpebral fissure was larger than the right. Left hemiparesis was present, most marked in the leg, accompanied by face and tongue weakness. There was generalized hypotonia with slight increase in reflexes on the left side and questionable Babinski and Hoffman signs on the same side. Abdominal reflexes were absent bilaterally. Sensation was difficult to test but a left hemisensory syndrome appeared to be present. A diffuse mottled brown pigmentation with several papillomata was noted on her body.

Laboratory Data. Cerebrospinal fluid: initial pressure, 380 mm. of water; Pandy, 4 plus; total protein, 139 mg. per cent; cells, 10 red blood cells and 8 lymphocytes per cu. mm.; Ayala index, 2.1. The Wassermann and colloidal gold tests in the cerebrospinal fluid were negative. Blood count, blood chemistry, and blood serology were normal. Urine analysis, 2 plus acetone. Electroencephalography was reported as suggestive of a deep lesion in the anterior part of the right hemisphere accompanied by considerable generalized edema.

Course. Following dehydration therapy, the patient's mental state improved and the grasping movements ceased. At this time it was learned that at times during her illness she would sense sewer-like odors. A ventriculography performed two days after admission showed a displacement of the ventricular system to the left

¹ The first six cases were presented in previous issues of the Journal (Vol. VII, No. 5 and 6).

with a dilatation of the left lateral ventricle. There was an indentation of the floor of the anterior horn of the right lateral ventricle. The appearance suggested a right subfrontal tumor. A fronto-temporal craniotomy following this procedure revealed a large tumor, measuring 5 x 4 cm. attached to the bone and dura in the right subfrontal region, apparently infiltrating the right hemisphere and crossing the midline. A subtotal removal of the tumor was performed. The patient never fully recovered consciousness and died on the tenth postoperative day.

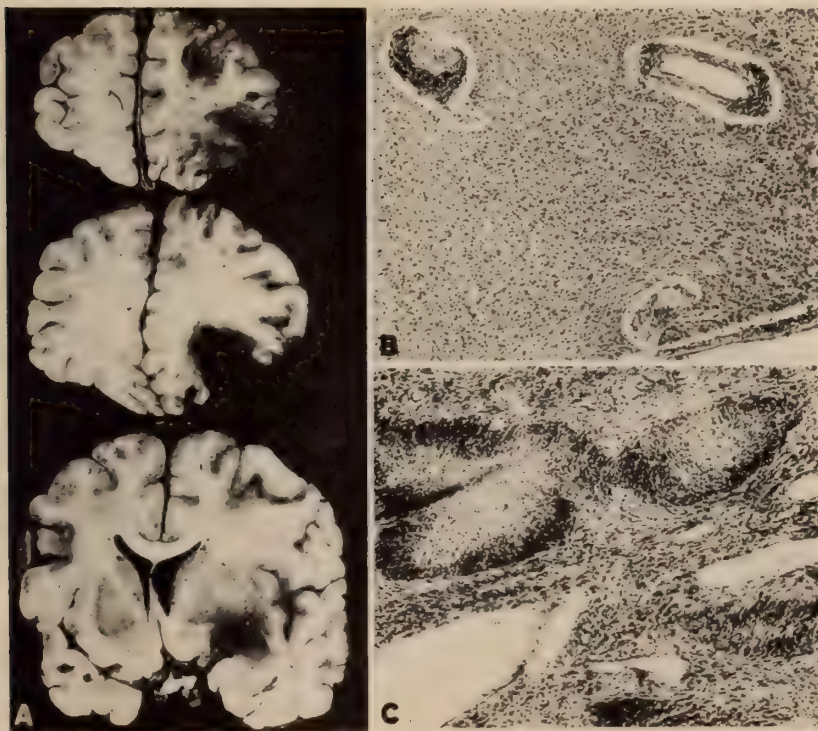


FIG. 10. Case 7. A. Coronal sections of the brain showing tumor in the right frontal lobe.

B. The extreme cellularity of the tumor with unripe cells grouped about blood vessels, (photomicrograph, hematoxylin and eosin stain).

C. Rows of tumor cells arranged around areas of homogenized tissue, (photomicrograph, hematoxylin and eosin stain).

Necropsy Findings. Brain. Gross. A coronal section of the brain, about 3 cm. in back of the frontal pole, shows two fairly large areas of discoloration, one near the dorsal border measuring about $1\frac{1}{2}$ cm. in diameter; another more irregular and wider in extent occupies the lower half of the frontal area at the same level (fig. 10A). These areas of discoloration show marked reduction in consistency and at present it is difficult to say whether they are the result of surgical trauma, alterations in the overlying meninges, or extensions of a neoplasm. Further back about 2 cm. posterior to the frontal pole an obvious asymmetry of the two hemispheres, with the right being much larger than the left, becomes apparent. The subcortex is wider and shows evidence of edema. In a triangle a short distance from the ventral extension of the dorsal longitudinal fissure there is another area of discoloration which

is the continuation of the second one described above. Here the color is a dark reddish-brown and the consistency of this area, which measures at its widest diameter about 3 cm., is increased. Tracing this area further backward it merges with the area of brownish discoloration of a lighter hue, which can be traced back as far as the point on the level of the optic chiasm occupying a space directly below the anterior commissure and extending into the temporal lobe. There is a marked deformity of the lateral ventricles: the anterior horn on the right side is displaced downward and widened while the anterior horn on the left side is on a higher plane, maintaining a somewhat normal outline. The bodies of both lateral ventricles are fairly symmetrical but displaced to the left. The third ventricle is exceedingly narrow, shows a concavity to the left and is also displaced to the left.

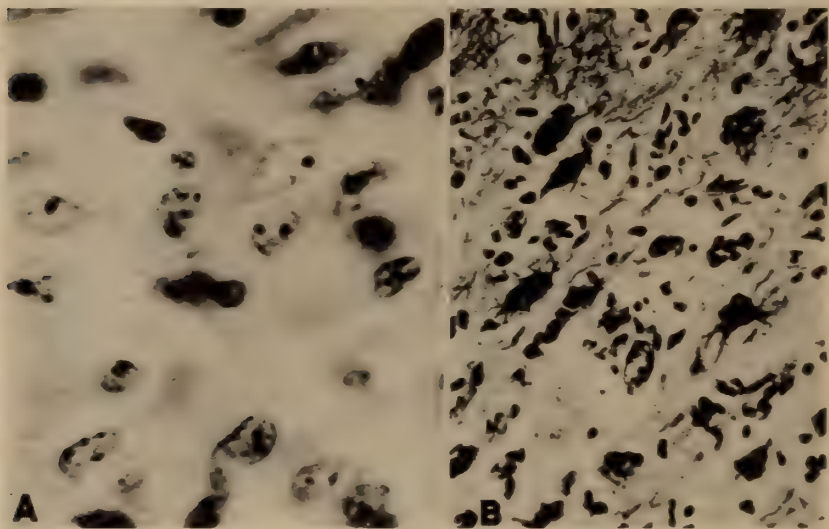


FIG. 11. Case 7: A. Neuroblasts, (photomicrograph, Nissl stain).

B. Atypical glial cells (photomicrograph, Hortega impregnation method, Globus modification).

Microscopic. Sections of the tumor, stained by the various neurohistological techniques, show a richly cellular and vascular tumor. Striking are the numerous perivascular aggregations of undifferentiated neuroectodermal cells. These aggregations vary in density, size, and arrangement about the blood vessels (fig. 10B). In some areas the tumor cells form dense palisades about less cellular cores (fig. 10C). Among the perivascular aggregations and throughout the tumor there are numerous neuroblasts in various stages of differentiation (fig. 11A). Usually the Nissl substance of these is not yet present and often there are two nucleoli within a single nucleus. The special silver stains disclose large cells with numerous short processes (fig. 11B). These cells at times appear to be both glial and neuronal in type and would seem to be a hybrid variety of glio-neuronal cell.

Comment. Dr. Globus: Of significance in this case is the rather short clinical course, a feature quite typical of the malignant form of a primary brain tumor. The hallucinatory episodes are also frequently encountered in the malignant form of brain tumor in which unripe neural elements are present in large numbers.

Anatomically, this tumor is a more malignant expression of the type of neoplasm described in Case 6 under the name of transitional glioneuroma.

Reported by *M. Sapirstein, M.D.*

Case 8. Neurospongioblastoma of the Left Cerebral Hemisphere

[From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen]

History (Adm. 439077; P.M. 11152). A man, 43 years of age, was admitted to the hospital on April 18, 1939. He was apparently well until two months before his admission, when early one morning, his wife was awakened by a cry emitted by her husband, whom she found passing through a generalized convulsion. During this episode which lasted about ten minutes he was unresponsive; and he remained confused for a few minutes before complete recovery. He could not recall any event in the episode. Subsequently new symptoms gradually appeared and advanced. He began to speak slowly and hesitantly; often he could not find the word he wished to use, and would have difficulty in naming objects. He became unable to concentrate on reading and became a poor speller. His personality changed; he became a quiet and morose person whereas he had formerly been jolly. It was noticed that his voice had become somewhat higher pitched. He began to be troubled by severe constipation. Ten days before admission he began to experience lancinating pains on the left side of his face, especially about the eye, and soon thereafter severe dizziness set in and he would not stand up alone.

Examination. The patient seemed to be well oriented in all spheres; he realized that since the onset of his illness there had been a considerable change in his speech and emotional reaction. His voice was hoarse. He spoke hesitantly and was often unable to express himself. In writing to dictation, he frequently misspelled and perseverated. He copied inaccurately and would substitute letters. His mathematical ability, however, was unimpaired. In walking, the right arm swung less freely than the left. There was a tenderness to percussion in the left fronto-temporal region. There was a blurring of the nasal margins of the discs with fullness of the veins. Both pupils were slightly irregular, the right was smaller than the left, and both reacted better in accommodation than to light. There was a slight weakness of the right face and of the right hand. The deep tendon and the superficial reflexes were active and equal. A positive Chaddock sign was obtained on the right side. The right upper extremity displayed a slight dysmetria while the right lower extremity was somewhat awkward in performing the heel-to-knee test. There was a questionable diminution in vibration sense in the right foot. Position sense appeared to be disturbed in the toes of the right foot. Two point discrimination was diminished in the fingers and toes on the right side.

Laboratory Data. Cerebrospinal fluid: clear; initial pressure, 140 mm. of water; dynamics, normal; Pandy, 2 plus; cells, 1 lymphocyte per cu. mm.; total protein, 62 mg. per cent; chlorides as sodium chloride, 700 mg. per cent; Wassermann and colloidal gold tests, negative. Electroencephalography disclosed abnormal potentials seeming to have origin in the left frontal region. This reaction was unchanged

after the intravenous administration of 50 per cent sucrose solution as an anti-edematant. X-ray examinations of the chest, abdomen, and skull were reported as essentially normal.

Course. The diagnosis of a tumor of the left hemisphere in the fronto-temporal region was the first to be made. Then when more emphasis was put on the dominance of sensory over motor signs, the lesion was allocated to the parieto-temporal lobe. During the patient's stay in the hospital his symptoms and signs varied. Once there was a brief period of confusion. For a short while his ability to speak and to read improved. Then his anomia became more marked and perseveration in speech set in. Meanwhile his ability to write improved. The deep reflexes in the

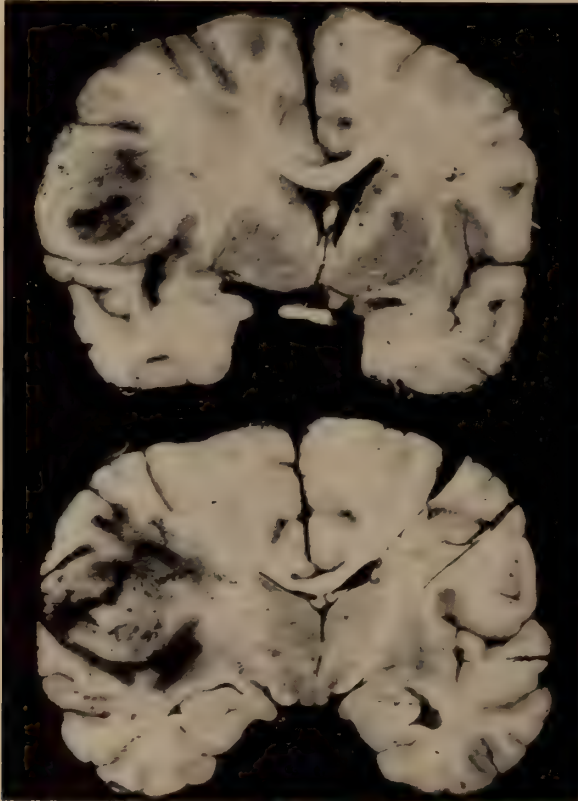


FIG. 12. Case 8. Coronal section of the brain showing the tumor in the left cerebral hemisphere.

right upper limb became hyperactive and the right upper abdominal reflex became diminished. His hoarseness was explained by chronic laryngitis secondary to sinusitis as reported by the otolaryngologist.

Eleven days after admission the patient was subjected to an encephalography. This disclosed a marked displacement of the ventricular system. The left lateral ventricle was deformed and somewhat compressed. The appearance was considered suggestive of a parasagittal lesion in the posterior parietal area. Two days after this procedure the weakness in the right upper limb began to progress; the deep

tendon reflexes became more active in both right limbs and some diminution in pain sensitivity was found over the right chest and abdomen.

A craniotomy was performed fourteen days after admission. Inspection, palpation and needle exploration yielded no evidence of a tumor and the cortex was not incised.

Following the operation, he was restless; then aphasia increased and drowsiness set in. A right hemiparesis appeared. The pupillary reactions remained normal. Incontinence set in, bilateral Babinski signs appeared, and his temperature rose to 103°F. A diagnosis of postoperative hemorrhage was made and reexploration was performed. About one ounce of extradural clot, chiefly temporal in location, was found and removed. The underlying brain tissue was edematous and the skin flap

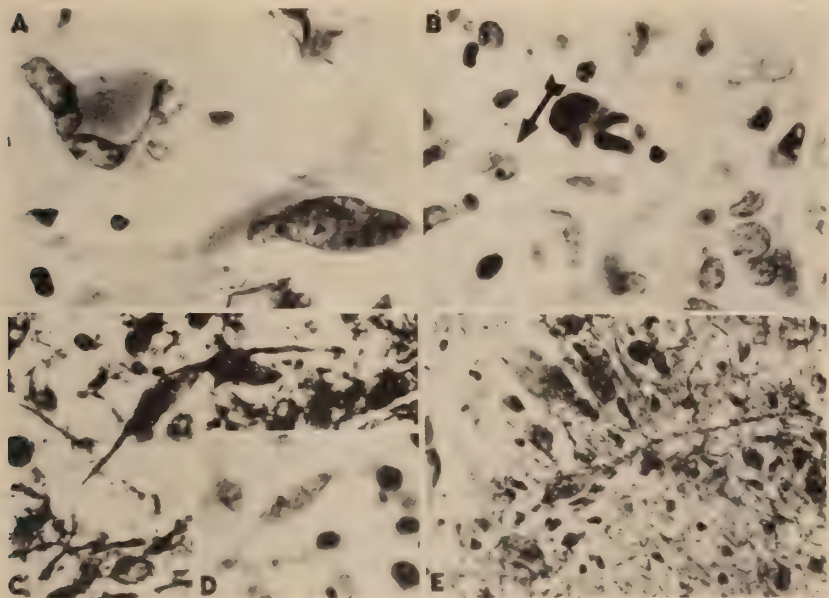


FIG. 13. Case 8. A. Two giant tumor cells, (photomicrograph, Hortega impregnation, Globus modification).

B. Young neuroblasts, see arrow, (photomicrograph, Nissl stain).

C, D and E. Bipolar neuroblasts, (Hortega impregnation method, Globus modification, C; Nissl stain, D; and Bielschowsky impregnation method, E).

was closed without the bone flap. The patient's temperature continued to rise, and he died six hours after the reexploration with a terminal temperature of 109°F.

Necropsy Findings. Brain. Gross. At the operative site there was a blood clot about 1 cm. thick. The underlying brain showed a reddish discoloration.

The left cerebral hemisphere was larger than the right. Sectioning of the brain disclosed that this enlargement was due to the presence of a tumor with a considerable degree of edema about it (fig. 12). The tumor mass occupied the frontoparietal region of the left hemisphere. It was quite circular in cross section and somewhat elliptical in its antero-posterior diameter. It extended from about the anterior limit of the precentral gyrus posteriorly to about the posterior termination of the supramarginal gyrus, measuring about $3\frac{1}{2}$ cm. in its long diameter.

It was situated near the surface of the hemisphere and ventrally was separated from the lateral fissure by a very narrow rim of brain tissue. It replaced the operculum almost completely and depressed the island of Reil. Except for yellow coloration in adjacent tissue, there was no clear-cut separation of tumor tissue from the adjacent brain tissue.

In the midbrain there was a wide area of reddish discoloration in the tegmentum near the midline and an area of brownish discoloration in the left peduncle within and extending slightly above the substantia nigra.

The arteries at the base of the brain were somewhat arteriosclerotic.

Microscopic. Sections of the tumor, stained by the various neurohistologic methods, disclose a richly cellular and vascular tissue. The tumor cells tend to occur in groups and streams. Perivascular aggregations of small round cells are seen, tending to occur scattered outward from the vessel wall where they are mingled with elongated tumor cells that are arranged radially about the vessels. With higher magnifications, glial and neuronal elements at all levels of differentiation are noted. There are multinucleated giant cells (fig. 13A), mononuclear undifferentiated neuroectodermal cells and neuroblasts (fig. 13B), the latter often occurring about blood vessels, bipolar neuroblasts, and fairly mature appearing nerve cells which are large and display long processes (figs. 13C, D, E). There are also nests of atypical cells (resembling the heterotopia of tuberous sclerosis) and occasional large cells suggestive of atypical nerve cells in that they contain a neuronal nucleus and are surrounded by satellitic ("capsule") cells.

The tumor tissue resembles the spongioblastoma multiforme except that there is a sharing of dominance between both glial and neuronal cell types. Hence this tumor type is classified as a neurospongioblastoma multiforme.

Comment. *Dr. Globus:* In this case again one is struck by the brevity of the clinical course and the onset with a convulsive seizure. The recognition of the existence of a neoplasm and the identification of its location presented no difficulty. It could almost at once be realized that the tumor was malignant and that surgical intervention offered practically no hope for a substantial recovery and little for the prolongation of life. The case raises the question whether the time is not ripe for utilizing an available method of recognizing the histologic character of tumor and guided by such information take the resolute position not to intervene by means of radical surgery.

Reported by *J. M. Zucker, M.D.*

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Effect of Carbohydrate and Fat in the Diet on Uric Acid Excretion. D. ADLERSBERG AND M. ELLENBERG. J. Biol. Chem. 128: 379-385, April 1939.

A high fat diet diminishes the uric acid excretion in normal individuals. Neither acidosis nor ketosis is of importance in this connection, since these factors were controlled by sufficient amounts of carbohydrate in the diet. A high carbohydrate diet, calorically equivalent to the high fat diet, does not depress the uric acid elimination. The factor responsible for the decrease in uric acid excretion in the urine of subjects on a high fat diet is not the increased caloric intake, but is the high fat content itself. These observations support the use of a high carbohydrate, low fat, as well as a low purine diet in the treatment of the uric acid diathesis.

Treatment of Rickets and Tetany with Single Massive Dose of Vitamin D. H. VOLLMER. J. Pediat. 14: 491, April 1939.

Rickets and tetany can be cured by peroral administration of one single dose of 600,000 units of vitamin D. The curative effect of this treatment is more prompt than that obtained with the daily administration of small doses. Serum calcium and serum phosphorus become normal and roentgenographic evidence of calcification shows within one week. The most impressive effect is the rapid rise of serum calcium. Tetanic convulsions did not recur after vitamin D shock therapy, and all other symptoms of hyperirritability disappeared usually within two days without any additional therapy.

The following conditions may be considered as indications for vitamin shock therapy: neonatal and infantile tetany, severe rickets, rickets associated with pneumonia or pertussis, rickets associated with chronic infections, and indifference of the parents of a rachitic or tetanic child. No contraindication seems to exist. No toxicity was manifested in 150 children treated with massive doses of vitamin D.

The proper dosage is 600,000 units, incorporated in milk. Vitamin D is effective also when administered parenterally.

The possibility of a successful vitamin D shock prophylaxis over the entire winter period with a single dose of 400,000 to 600,000 units is discussed.

Serum Calcium in the Newborn. B. S. DENZER, M. REINER AND S. B. WEINER. Am. J. Dis. Child. 57: 809-816, April 1939.

A study of the calcium level in the cord blood and of the blood calcium curve of the neonatal period has been made. There is a distinct drop in the calcium level of the blood during the first four days of life, with a subsequent slow rise to a point slightly above the average level of later infancy. This depression of the calcium

content is not related to race, weight at birth, or neonatal loss of weight. The inorganic phosphorus content of the blood during the neonatal period is higher than the phosphorus content of the cord blood but shows no definite constant curve. The protein level of the blood remains constant during the neonatal period and therefore cannot affect the level of the available ionizable calcium. The data derived from a comparison of calcium and phosphorus curves in the neonatal period do not supply an adequate explanation of tetany neonatorum.

Treatment of Internal Hemorrhoids by Injection; a Study based on Observations of 5000 Injections. A. W. M. MARINO AND R. TURELL. Brooklyn Hosp. J. 1: 93, April 1939.

This study based on 5000 injections, showed that injectional therapy when used with discretion and applied to properly selected cases has a well deserved place in the therapeutics of hemorrhoids. The procedure should be restricted to the treatment of uncomplicated, soft, bleeding, and moderate sized prolapsing, but easily reducible piles. The contraindications, dangers, and the technic of injection are described in detail. Properly performed injections should not result in complications. In six per cent of the cases there was a definite recurrence of the internal hemorrhoids. In certain instances where hospitalization is undesirable or when hemorrhoidectomy cannot, or should not, be performed, injectional therapy may be elected.

Injectional therapy is useful in the early months of gestation. Urea and quinine hydrochloride should not be employed for obvious reasons.

The method of treatment of hemorrhoids by injection is not without danger. Surgical judgment as well as skill are essential, for although the method seems simple, unless one understands the rationale and technic, disappointment and complications may result.

Observations Concerning Absorption of Sulfanilamide from Large Intestine in Man; an Experimental Study. R. TURELL, A. W. M. MARINO AND L. NERB. Brooklyn Hosp. J. 1: 90, April 1939.

In a previous investigation, it was found that sulfanilamide introduced into the rectum of rabbits is rapidly absorbed. In the present communication the results of studies on the absorption of a one per cent solution of sulfanilamide from the human colon and rectum are recorded. A series of eight normal individuals who received rectal instillations of a one per cent solution of sulfanilamide showed the presence of the drug in the blood. In order to determine whether the drug is absorbed directly from the rectum or colon or whether it must pass to the ileum before being absorbed, the same investigation was repeated in a patient who three years previously had had an ileostomy with exclusion of the colon. It was demonstrated that absorption of sulfanilamide took place from the isolated colon. The foregoing experimental studies showed that adequate concentrations of sulfanilamide can be maintained in the blood by means of rectal instillations of a one per cent solution of sulfanilamide. The rectal route of administration is recommended when sulfanilamide cannot be given by mouth.

Temperature Changes in Skin and Muscle of Lower Extremities Following Intravenous Injections of Typhoid Vaccine. M. FRIEDLANDER, W. BIERMAN AND S. SILBERT. Proc. Soc. Exper. Biol. & Med. 41: 221, May 1939.

Fever was produced in humans by the intravenous injection of typhoid vaccine. The rise in body temperature was accompanied by a gradual fall in calf muscle temperature. These changes were unaltered by the occurrence of chills and tremors. The skin surface temperature rose before the onset of the chill but dropped when the chill occurred.

Angina Pectoris and Cardiac Infarction from Trauma or Unusual Effort. E. P. BOAS. J. A. M. A. 112:1887, May 13, 1939.

Twenty-seven cases of cardiac infarction or the syndrome of angina pectoris immediately following a non-penetrating injury to the precordium or unusual bodily effort are reported.

When a person previously free from symptoms of coronary artery disease has such symptoms after an injury to the chest or unusual physical exertion, the heart disease may be attributed to these external factors. When a person with simple angina pectoris has coronary artery occlusion following such injury or effort the sudden progression of the lesion may be ascribed to these causes. When such a sequence of events occurs in a person gainfully employed while he is at his task, it is proper to conclude that the cardiac disability is compensable, provided the cardiac symptoms accompany or follow immediately on the event to which the cardiac injury is ascribed and provided there is a continuity of symptoms dating from the event to the time of complete disability. Such disability may be delayed by several days or weeks.

The Use of Sulfanilamide in Surgery of the Colon and Rectum. H. GARLOCK AND G. P. SELEY. Surgery, 5:787, May 1939.

The authors, as a result of their experience, have come to the conclusion after a careful evaluation of the clinical course of a group of patients, that the postoperative phase has been singularly uncomplicated, the morbidity has been unusually slight, and peritonitis has been nonexistent. In this connection it is important to note that, in 21 consecutive cases, streptococcus hemolyticus was not recovered in any of the cultures made. It is realized that the number of cases reported herewith is not sufficient to warrant definite conclusions. However, the impression gained is that the results obtained so far warrant a continuation and extension of this study.

The Attitude of the Psychoneurotic Toward Scientific Contraceptive Advice. J. H. FRIEDMAN. J. Nerv. & Ment. Dis. 89:672, May 1939.

A study was made of forty psychoneurotics who attended a mental hygiene clinic and who were referred to a birth control clinic. Only one patient was benefited by the contraceptive advice. The writer concludes that where anxiety and other neurotic symptoms in regard to contraception exist, they are part of a more deep seated conflict in regard to sexuality as a whole, pregnancy, and contraception, as psychological problems. Thus, blunt proposal of contraceptive advice to such individuals will not relieve the cause of the anxiety or the other neurotic symptoms. If preparation is not given through a careful approach of the topic and consideration of all the factors (sociological, religious, and psychological) involved, the patients are likely, consciously or unconsciously, to evade application of the knowledge given them.

The Female Sex Hormones. R. T. FRANK. New England J. Med. 220: 821, May 18, 1939.

The anatomy, physiology, and finally the chemistry covering the sex cycles has been gradually clarified. The close chemical relationship of the male and female hormones became known, and biological reactions to demonstrate the hormonal actions were eventually developed.

An analysis of the sex cycle in the female has shown an abortive (menstrual) and a fertile (pregnancy cycle). The primary agent is the anterior pituitary, and under its influence, follicular and corpus luteum phases affect the uterus and breasts. In addition to the normal, both over and underfunction has been demonstrated. Overfunction usually shows itself as menorrhagia, metrorrhagia, or premenstrual tension. Underfunction produces amenorrhea, dysmenorrhea and sterility. In pregnancy

the hormone conditions show huge elevation of levels. In the menopause, excess of gonadotropic hormone is the rule. Based on these increases in our knowledge, considerable advance in endocrine therapy has been achieved.

Extrapleural Pneumonolysis in the Treatment of Pulmonary Tuberculosis. H. AUFSES. *Medicine*, 18: 129, May 1939.

A review of the entire literature on extrapleural pneumonolysis including anatomy, technique, indications, mode of action, and effect on respiration is presented. "Simple" pneumonolysis as well as pneumonolysis with temporary and permanent tamponade are also discussed. The use of fat and muscle implants is reviewed together with the results obtained. An analysis of 1144 cases of "paraffin plombe" collected from the literature is included. The various methods of pneumonolysis in conjunction with thoracoplasty are discussed.

Because of the present interest in extrapleural pneumothorax, this procedure is carefully reviewed both from the standpoint of earlier attempts and present day reports.

A bibliography of 211 references is included.

Biophotometric Studies in 30 Cases of Chronic Ulcerative Colitis. H. H. LERNER AND H. G. RAPAPORT. *Am. J. Dig. Dis.* 6: 239, June 1939.

A study of avitaminosis A by means of the biophotometer in 30 cases of chronic ulcerative colitis revealed that 1.41 per cent have a subclinical deficiency (twice the "normal" expectancy). The high percentage of avitaminosis A in the interval and healed phases indicates the need of larger doses of vitamins prophylactically. Acutely ill patients receiving massive doses of vitamin A show normal dark adaptation. Chronically ill patients show deficient dark adaptation. There appears to be more than a casual relationship between avitaminosis A and ulcerative colitis. The ability to absorb vitamin A given in normal amounts is diminished in ulcerative colitis.

Evaluation of the Tuberculin Patch Test (Vollmer and Lederle). H. VOLLMER AND E. W. GOLDBERGER. *Am. J. Dis. Child.* 57: 1272, June 1939.

A comparative study of the tuberculin patch test (Vollmer-Lederle) and the Mantoux test has been carried out on 678 children.

Among 417 children admitted to the wards of The Mount Sinai Hospital, the reliability of the tuberculin patch test as compared with the Mantoux test performed with 0.1 mg. of old tuberculin was 100 per cent.

Two hundred and sixty-one tuberculous children of the Sea View Hospital showed 100 per cent conformity between the tuberculin patch test and the Mantoux test with first strength solution of purified protein derivative or 0.01 to 1 mg. of old tuberculin.

Consequently it seems that the Mantoux test with 0.1 mg. of old tuberculin or less or with first strength solution of purified protein derivative can safely be replaced by the tuberculin patch test.

A routine is suggested for tuberculin testing, the tuberculin patch test being proposed as the first test.

The Value of Sulfanilamide in Orogenous Infections. L. MAYBAUM, E. SNYDER AND L. COLEMAN. *J. A. M. A.* 112: 2589, June 24, 1939.

In this paper, the authors state that the use of sulfanilamide has resulted in a genuine advance in the treatment of certain otogenous infections. Exenteration of the otitic focus is of paramount importance. Indiscriminate use of the drug may obscure the diagnosis or result in a masked or latent clinical picture of mastoid involvement. Under sulfanilamide therapy, the usual clinical course of an otitic complication may be modified.

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CONTENTS

	PAGE
THE ANALOGUES OF VITAMIN K: THEIR CLINICAL USEFULNESS. <i>Albert M. Snell, M.D.</i>	67
THE PRESENT STATUS OF VITAMIN K THERAPY. <i>S. S. Lichtman, M.D., and John H. Garlock, M.D.</i>	76
A CASE OF XANTHINE CALCULI. <i>A. Hyman, M.D., and H. E. Leiter, M.D.</i>	84
SPONTANEOUS PNEUMOTHORAX SIMULATING ACUTE CORONARY OCCLUSION. <i>Arthur M. Master, M.D., Henry H. Kalter, M.D., and Simon Dack, M.D.</i>	89
CYSTIC TUMOR OF THE FOURTH VENTRICLE. <i>Joseph M. Zucker, M.D., and E. Pumpian Mindlin, M.D.</i>	92
OTOGENOUS TETANUS. <i>Samuel Rosen, M.D.</i>	96
EARLY DIAGNOSIS OF OTITIC MENINGITIS IN CHILDREN. <i>Samuel M. Bloom, M.D.</i>	98
TRANSIENT GLOBAL APHASIA AND HALLUCINATORY EPISODE IN NEUROSYPHILIS. <i>Daniel Stats, M.D.</i>	101
CLINICAL PATHOLOGICAL CONFERENCE.....	107
CLINICAL NEUROPATHOLOGICAL CONFERENCE.....	112
OBITUARY. <i>George Blumenthal</i>	115
ABSTRACTS.....	117

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THE ANALOGUES OF VITAMIN K: THEIR CLINICAL USEFULNESS¹

ALBERT M. SNELL, M.D.

[Division of Medicine, Mayo Clinic, Rochester, Minnesota]

The introduction of vitamin K to clinical medicine came as a result of the observations of Dam and his associates (1), who showed that a deficiency disease resembling scurvy could be produced in chicks by a diet deficient in certain fat-soluble ingredients. They and other investigators also demonstrated that the condition could be cured by the administration of an antihemorrhagic material present in the nonsaponifiable, nonsterol portion of hog liver fat, in hemp seed, in certain cereals and in vegetables. It was shown later by the Danish investigators (2) that deficiency in this fat-soluble component resulted in diminution of the amount of prothrombin in the circulating blood, eventually leading to fatal hemorrhagic diathesis. The deficient factor was called vitamin K after the Danish word "Koagulations Vitamin."

Quick and his associates (3) seem to have been the first to suggest that deficiency in vitamin K might be a factor in the production of the hemorrhagic diathesis of patients with obstructive jaundice, and they also demonstrated that there was deficiency of prothrombin in the blood of such patients. Fortunately for clinical investigators of the subject, Smith and his associates (4) at the University of Iowa had collected a mass of information in years of study on the subject of prothrombin, and it was possible for them to put their information to good use in the investigation of the disease processes which have been mentioned. Within a relatively short time various workers in this country and abroad demonstrated that vitamin K was a specific remedy for prothrombin deficiency occurring under certain circumstances, as follows: a) primary dietary deficiency in respect to the antihemorrhagic (5) vitamin; b) secondary deficiency concurrent with obstructive jaundice by virtue of the fact that exclusion of bile from the intestine interfered with absorption of this fat-soluble (6) vitamin; c) secondary deficiency associated with certain gastro-intestinal diseases, especially those which result in a loss of continuity of the intestine or destruction of absorptive (17) surfaces; d) prothrombin deficiency in primary hepatic disease; this lack is not primarily attributable to deficiency in vitamin K; the difficulty seems to lie in the inability of the injured liver to

¹ Presented April 18, 1940 at the Blumenthal Auditorium of The Mount Sinai Hospital as part of the Symposium on Vitamins.

manufacture (4, 8) prothrombin, and e) the physiologic hypoprothrombinemia of the newborn (9).

Thus, within a relatively short period a considerable field of clinical usefulness was found for the antihemorrhagic material first discovered in a study of deficiency disease in chicks. From the time that reports of the first clinical observations appeared, biochemists studied the crude materials containing the vitamin in the hope of discovering its chemical nature. Their search was pursued the more vigorously because of the need for a readily available product which could be given parenterally or administered by mouth in a palatable form. The early concentrates of vitamin K used at the Mayo Clinic were prepared from putrefied fish meal and were objectionable on a good many counts, but chiefly because of the taste and odor and the difficulty of introducing the material in any quantity into the gastro-intestinal tract of seriously ill patients.

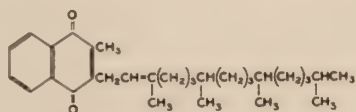
CHEMISTRY OF VITAMIN K

In 1939, preliminary studies on the probable structure of vitamin K were reported in this country by McKee and his collaborators (10) and in Europe by Dam, Karrer and others (11). These early reports indicated that the vitamin probably had a quinoid structure. A few months later, Binkley and his associates (12) and, independently, Fieser and his co-workers (13) reported on the structural formula of vitamin K₁. They demonstrated conclusively that the composition of this vitamin was represented correctly by the formula, 2-methyl-3-phytyl-1,4-naphthoquinone. They were able to prepare the material by a process of synthesis and to demonstrate its antihemorrhagic activity. Later, Binkley and others (14) prepared vitamin K₂, a related compound, from putrefied fish meal. This material, which has not yet been synthesized, was found to be a 2,3-disubstituted naphthoquinone, a thirty carbon side chain with six double bonds attached at the three position (fig. 1).

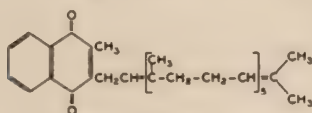
After the first announcements of the probable quinoid structure of the vitamin, chemists and biologists naturally turned to the large series of known substances having quinoid nuclei and began the study of them with reference to their possible antihemorrhagic activity. Almquist and Klose (15, 16) were the first to report that phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) possessed physical and biologic properties similar to those of pure vitamin K. This material was investigated clinically (17) also and was found to possess antihemorrhagic activity in cases of obstructive jaundice. These investigators suggested that phthiocol was perhaps the simplest member of an homologous series of antihemorrhagic substances of related composition.

Ansbacher and Fernholz (18) demonstrated that a closely related compound, 2-methyl-1,4-naphthoquinone, had an even greater degree of antihemorrhagic potency than phthiocol, and their observations were sub-

sequently confirmed by numerous investigators. At least two other compounds of similar composition which have the advantage of being water soluble have been tested clinically and found therapeutically useful. One of these is 1,4-dihydroxy-2-methyl-3-naphthaldehyde, which was prepared in Doisy's laboratory; another, prepared by Emmett and his associates (19), is an even simpler compound, 4-amino-2-methyl-1-naphthol hydrochloride. The structure of these four closely related compounds



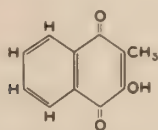
Vitamin K₁
(2-methyl-3-phytyl-1, 4-naphthoquinone)



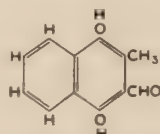
Vitamin K₂ (Tentative formula)

From Doris, Binkley and associates

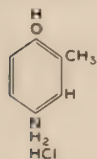
Fig. 1. Chemical structure of vitamins K₁ and K₂



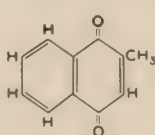
2-methyl-3-hydroxy-1,
4-naphthoquinone



1,4-dihydroxy-2-methyl-
3-naphthaldehyde



4-amino-2-methyl
naphthol hydrochloride



2-methyl-1,
4-naphthoquinone

FIG. 2. Chemical structure of some synthetic analogues of vitamin K

having antihemorrhagic activity is represented in figure 2. Since these four compounds have been submitted for clinical use, several other quinoid substances have been subjected to analysis and have been tested on chicks subsisting on diets deficient in vitamin K. The relative activity of these various compounds has been studied particularly by Almquist and Klose (20), to whose reports the reader is referred for details.

Synthetically prepared vitamin K₁ has been used in the treatment of prothrombin deficiency with satisfactory results (21). The available data are insufficient to warrant general conclusions, but it would appear that

this preparation is less active and not so rapidly utilized as is the simpler compound, 2-methyl-1,4-naphthoquinone.

The essential features of all of the more active antihemorrhagic preparations may be characterized as follows: a) A naphthalene ring structure; b) a methyl group in the two position; c) quinone-oxygen at positions one and four; d) a double bond between carbon atoms two and three. The side chains which appear in the three position in naturally occurring vitamins K₁ and K₂ are not essential to the activity of these compounds.

ANALOGUES OF VITAMIN K AVAILABLE FOR CLINICAL USE

Of the four compounds which appear in figure 2, only two have been widely used clinically; both are as active as vitamin K₁, or even more so when considered on a molar basis. These two compounds are 2-methyl-1,4-naphthoquinone and 4-amino-2-methyl-1-naphthol hydrochloride. The first mentioned compound is easily prepared, is relatively stable, and is so constant in its action that its use has been suggested as a standard for the comparison of vitamin K activity of all related compounds. The original compound is not water-soluble, and hence is not available for parenteral administration. It is, however, possible to use a water-soluble preparation, namely 2-methyl-1,4-naphtholhydroquinone-3-sodium sulfonate (22). This material is suitable for parenteral administration and may also be absorbed from the intestinal tract in the absence of bile salts. It is of interest to note that 2-methyl-1,4-naphtholhydroquinone diphosphoric acid ester is even more potent on a molar basis than methyl naphthoquinone. Almquist and Klose (20), who made this observation, suggested that phosphorylation may represent a step in the normal metabolism of the antihemorrhagic quinones. Another derivative of methyl quinone which also has been studied is the potassium salt of the disulfuric acid ester of 2-methyl-1,4-naphthoquinone. Flynn and Warner (23) have shown that this compound is effective in preventing hemorrhage in jaundiced rats which are receiving diets deficient in vitamin K. Smith and Owen (24) also have shown the effectiveness of the water-soluble hydrochloride of 4-amino-2-methyl-1-naphthol when given by mouth to patients who have obstructive jaundice. The use of phthiocol has been abandoned chiefly because of the relatively low potency of the compound, and the naphthaldehyde compound, previously mentioned, has not thus far been prepared for use on a large scale.

FACTORS TO BE CONSIDERED IN CLINICAL USE OF ANALOGUES OF VITAMIN K

It is probable that owing to bacterial activity the gastro-intestinal tract of mammals contains some form of vitamin K. The presence of this vitamin would explain the rise in the quantitative level of prothrombin when bile or bile salts are given to otherwise untreated patients who have obstructive jaundice. As Smith and Owen (24) have pointed out, the

average diet or the average content of the intestinal tract probably does not contain any great amount of water-soluble compounds having vitamin K activity, for otherwise signs of deficiency of vitamin K would not develop so readily in cases of obstructive jaundice.

As mentioned in an earlier paragraph, general therapeutic use of the crude concentrates having vitamin K activity was difficult because of their taste, odor, solubility and physical properties. Difficulties also arose when the vitamin was urgently needed for emergency use. As experience with the various clinical types of prothrombin deficiency increased, the need for a soluble and rapidly acting analogue of the vitamin became apparent. Some groups of investigators found that a precipitous postoperative fall in prothrombin occurred even though the jaundiced patients had had presumably adequate preoperative preparation with vitamin K concentrates and bile salts. This was true not only of patients who had obstructive jaundice and disease of the biliary tract but also of patients who had been subjected to various types of surgical procedures involving the stomach and the colon. In such cases of postoperative prothrombin deficiency, hemorrhage into the gastro-intestinal tract often developed rapidly and precluded in many instances the satisfactory oral administration of vitamin K concentrates.

The observations regarding postoperative deficiencies mentioned previously bring out clearly the fact that there is little stored vitamin K in the body, at least in a form available for rapid use. They also emphasize that, while prothrombin is present in amounts considerably in excess of those needed to form a clot of the circulating blood, there are no important body stores of this material which can be drawn on in emergencies.

The mechanics of the postoperative fall in prothrombin which is of such obvious clinical importance have been studied by Cullen and his associates (25). They found that chloroform anesthesia produced a marked fall in prothrombin, as one might expect, knowing the effects of this anesthetic on the parenchyma of the liver. When ether and cyclopropane were used, there was little or no effect on prothrombin which could be ascribed directly to the anesthetic. Lord (26) had previously shown that laparotomy on animals with vigorous massage of the liver produces a marked decline in prothrombin. Presumably, the factor of operative trauma is more important, therefore, than that of the anesthetic in the production of postoperative hypoprothrombinemia.

The vitamin K analogues which have just been mentioned are peculiarly well adapted to treatment of suddenly developing deficiencies of prothrombin. The compound, 2-methyl-1, 4-naphthoquinone, can be given orally with bile salts, or employed to much greater advantage in a form suitable for intravenous injection. When given by the latter route, this compound acts with extreme rapidity and in about two hours any danger from prothrombin deficiency has been eliminated. The compound, 4-amino-2-methyl naphthol hydrochloride is similarly effective.

The rapidity of action of these vitamin analogues proposes a difficult question for the biologic chemist: how do these materials act to form prothrombin? It hardly seems likely that they serve as a prosthetic group in the prothrombin molecule; a better suggestion is that they may act in some unknown manner as catalysts.

No one knows as yet how long the effect of parenterally administered naphthoquinones may last and what is the maintenance requirement of a patient who is not receiving any vitamin K in his food and has pronounced vitamin K deficiency. The problem is difficult, if not impossible, to solve in relation to human subjects. The excellent studies of Flynn and Warner (23) on jaundiced rats which have been maintained on diets deficient in vitamin K indicate that maintenance doses of these compounds are in the order of magnitude of 2 gammas twice daily for a rat weighing 250 gm. Their studies also indicate that 20 gamma doses given to these animals will increase the concentration of prothrombin from 5 per cent of normal to 80 per cent within twenty-four hours but that this level is not maintained long. Within three days the quantitative prothrombin level of some of the animals thus treated decreased to 20 per cent of normal. Flynn and Warner have further demonstrated, however, that with larger and continued doses a considerable degree of storage is maintained. The clinical application of these findings is obvious.

OBSERVATION ON CLINICAL RESULTS OBTAINED BY THE USE OF THE ANALOGUES OF VITAMIN K

Considerable experience with the use of crude vitamin K concentrates convinced most workers that there still was much to be desired in the way of therapeutic success. The suddenness and severity with which post-operative hemorrhage occurred, even when patients had been adequately prepared, precluded successful administration of the older compounds by way of the intestinal tract, and there were a certain number of postoperative deaths which could have been prevented had the more soluble and easily available preparations been available for general use. During the last year, however, the vitamin K analogues, mentioned previously, have been generally used on the surgical service in the Mayo Clinic with a resulting drop in mortality rate which is very gratifying. Walters and associates (27) recently reported that the mortality rate for all surgical procedures on jaundiced patients fell from 14.9 per cent in 1937 and 1938 to 6.4 per cent in 1939 and he credited these vitamin K analogues with a large part of this reduction. The saving in mortality was particularly conspicuous in a group of patients with carcinoma of the pancreas who were subjected to cholecystogastrostomy. In this group the mortality was reduced by half because of the general use of soluble vitamin K analogues. No exact figures are as yet available to indicate the decrease in mortality effected by these compounds in cases of other surgical procedures on the gastro-intesti-

nal tract but personal experience convinces us who have worked at the Mayo Clinic that a considerable number of lives have been saved.

The use of these compounds in cases of primary hepatic disease may be mentioned briefly. As was stated in an earlier paragraph, the prothrombin deficiency which occurs in these cases is due to failure of the liver to form prothrombin from vitamin K already present within the body. As the recent studies of Bollman and his co-workers (28) indicate and as those of Brinkhous and Warner (29) substantiate, no compound is likely to be completely successful in treatment of such patients. For example, Brinkhous and Warner have shown that the administration of vitamin K fails to modify in any way the fall in prothrombin following administration of chloroform or the rise in prothrombin during the recovery period. However, it appears that with large and continued doses the remaining functioning hepatic tissue may be able to maintain the quantitative level of prothrombin sufficiently high to prevent gross bleeding. For some patients under our observation, the long continued use of large doses of 2-methyl-1,4-naphthoquinone has been moderately successful in this connection and toxic effects have not been noted (30).

The effective use of quinoid substances having vitamin K activity in the treatment of the physiologic hypoprothrombinemia of the newborn warrants brief comment. It has been demonstrated that the prothrombin level of the newborn infant falls, beginning the second day after birth, and continues at a low level for most of the first week. In most instances the reduction in prothrombin is not sufficient to cause gross bleeding, yet it has been said that about 65 per cent of all infants dying during the first week of life present hemorrhages in some organ or organs. It is conceivable although not certain that this bleeding may be a result of prothrombin deficiency and, hence, it would seem desirable to recommend the routine use of naphthoquinones in the hope of correcting this condition. Vitamin K analogues suitable for parenteral administration may be administered to mothers during labor with a substantial effect on the prothrombin of the newborn. The same compound may be administered to infants if the prothrombin clotting time increases markedly. The full possibilities of this form of prophylactic treatment have yet to be investigated, but on theoretical grounds, at least, it would appear that the saving in infant mortality and morbidity might be considerable.

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THE PRESENT STATUS OF VITAMIN K THERAPY

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The present knowledge of the chemical structure of vitamin K and of the experimental and clinical evidence of vitamin K deficiency has been thoroughly reviewed recently by Brinkhous (1). However, the clinical aspects of vitamin K deficiency and the indications for vitamin K therapy require further study. This involves a knowledge of the circumstances leading to vitamin K deficiency, laboratory methods for the recognition of such deficiency and the influence of vitamin K on various types of bleeding.

THE MAJOR CAUSES OF VITAMIN K DEFICIENCY

Inadequate vitamin K intake. It is difficult to produce vitamin K deficiency in normal adults by dietary restrictions alone. This is attributed to the stored reserve of this substance and to the fact that intestinal bacteria are an additional source of supply. Nutritional vitamin K deficiency with prolonged prothrombin time was reported by Kark and Lozner (2) in four subjects suffering from scurvy due to prolonged restriction of fruits and vegetables. Esophageal or pyloric obstruction or the continuous aspiration by suction of the contents of the stomach and duodenum may also lead to vitamin K deficiency.

The impairment of absorption caused by defective absorptive intestinal surface. Intestinal obstruction, short-circuiting operations such as gastro-ileostomy which reduce the absorptive surface of the small bowel, and diseases associated with chronic diarrhea such as sprue, ulcerative colitis, dysentery, multiple strictures, or fistulas, have been shown to produce vitamin K deficiency.

The impairment of absorption due to lack of bile in the intestine. K-avitaminosis may result from lack of bile salts in the intestinal tract in obstructive jaundice and intrahepatic jaundice associated with deficient biliary excretion. The administration of bile salts alone cannot correct vitamin K deficiency (Zuckerman, et al. (14)).

Hepatic insufficiency preventing utilization of vitamin K. Organic and functional disease of the hepatic parenchyma may produce K-avitaminosis despite adequate intake and absorption of vitamin K. The liver is apparently intimately concerned in the conversion of vitamin K into prothrombin.

Repeated hemorrhage. This factor itself depletes plasma prothrombin and aggravates the effect of other causes of hypoprothrombinemia (Mateer (3)).

In the evaluation of the factors producing K-avitaminosis it is important, therefore, to establish which of the above factors alone or in combination is responsible for the deficiency in any particular case.

THE CLINICAL RECOGNITION OF VITAMIN K DEFICIENCY

The sole means of recognizing K-avitaminosis at present is the demonstration of hypoprothrombinemia. A number of practical procedures for the estimation of prothrombin time have been developed (Quick,¹ Brown and Bancroft (4); Warner, Brinkhous and Smith (5); Smith, Ziffren, Owen, Hoffman (6); Allen, Julian and Dragstedt (7)).

It is well recognized that the body normally possesses a reserve surplus of prothrombin. Critical reduction of prothrombin leading to free bleeding is fortunately not common. Before the advent of vitamin K therapy, surgeons had reduced the incidence of bleeding in obstructive jaundice materially by careful preoperative preparation of patients with multiple transfusions and with intravenous glucose therapy. When hemorrhage occurs, the estimation of the level of prothrombin in the blood constitutes, at present, the sole means of determining whether it is due to K-avitaminosis or to some other factor.

THE CORRECTION OF K-AVITAMINOSIS

Deficiency due to faulty intake or faulty absorption may be corrected by the oral or parenteral use of vitamin K or its substitutes.² K-avitaminosis resulting from serious liver dysfunction may be irreversible and completely fail to be corrected by any form of treatment. The restoration of normal liver function should be the immediate objective of treatment in all such cases.

¹ The Quick technique was used in the estimation of prothrombin time in all our cases. The tests were performed by members of the Hematological staff under the direction of Dr. Nathan Rosenthal.

² In the clinical use of vitamin K (in doses of 1 to 2 mg.) toxic effects have not been noted. All the oral preparations used were found potent. Klotogen (Abbott), the first natural product used, was found to be satisfactory. With the advent of naphthoquinone therapy, we employed 2-methyl-1,4-naphthoquinone in doses of 1 to 2 mg. in the form of Kagalin and Proklot (Lilly), and Kayquinone (Abbott). Our experience with parenteral therapy has been limited thus far to Hykinone (Abbott), an isotonic solution of the above named naphthoquinone given in doses of 2 mg. Andrus and Lord (8) favor the intramuscular use of this naphthoquinone in corn oil. For other naphthoquinone derivatives which have been successfully employed clinically, the reader is referred to the papers of Weir, Butt, and Snell (9) and Brinkhous (1).

Bile salts were administered orally in the form of Bilcin (Abbott) and Bilon (Lilly).

Successful vitamin K therapy. Success in vitamin K therapy may be obtained in cases of hypoprothrombinemia due to obstructive jaundice, disease of the gastro-intestinal tract (pyloric stenosis, ulcerative colitis, dysentery, etc.) and hemorrhagic disease of the newborn.

Multiple transfusions of whole blood, while temporarily effective in supplying prothrombin, do not correct K-avitaminosis.

Failures of vitamin K therapy. Failure of oral therapy with vitamin K or its substitutes occurs in the case of patients with serious impairment of liver function or with insufficient absorption of the vitamin from the intestinal tract. In the latter group, effective results may be obtained by parenteral administration of the vitamin. Failure of treatment by either oral or parenteral methods is noted in cirrhosis and other forms of hepatic degeneration. In our own series of cases vitamin K failed to modify hypoprothrombinemia in four fatal cases of portal and toxic cirrhosis in which the initial hypoprothrombinemia ranged from 35 to 70 per cent of normal. Failure of prothrombin response to vitamin K also occurred in two cases of prolonged obstructive jaundice caused by stricture of the common bile duct and carcinoma of the head of the pancreas; in these patients the prothrombin time approximated 60 per cent of normal (Quick method).

Parenteral versus oral vitamin K therapy. Observations in a patient with a neoplasm of the duodenum, previously treated elsewhere by duodeno-jejunostomy, who developed obstructive jaundice illustrate the indications for intravenous use of vitamin K. In this case, a marked prothrombin deficiency was raised from 34 per cent of normal to 87 per cent by a single intravenous dose of 2 mg. of vitamin K (Hykinone). In five days the prothrombin level had again dropped to 60 per cent of normal despite oral administration of the vitamin. A second dose of 2 mg. of vitamin K administered intravenously promptly raised the prothrombin level to 85 per cent of normal. Interference with absorption of vitamin K from the bowel because of the duodeno-jejunostomy and the obstructive jaundice caused by the neoplasm of the duodenum were probably responsible for the failure of prothrombin response to oral therapy (fig. 1).

In decompensated cirrhosis, vitamin K also proved ineffective except in one instance in which it eventually succeeded in producing a partial prothrombin response. In this type of case the factor of malabsorption of vitamin K because of bile salt deficiency is added to that of serious impairment of liver function.

The relationship of impairment of liver function to failure of vitamin K therapy. It is generally recognized that the prothrombin response to vitamin K therapy depends upon an intrinsic function of the liver. The degree of prothrombin response in vitamin K therapy has already been closely correlated with the results of the hippuric acid test (Wilson (10)). Andrus (11) has stressed the prothrombin response to vitamin K in hypoprothrombinemia as a sensitive index of liver function.

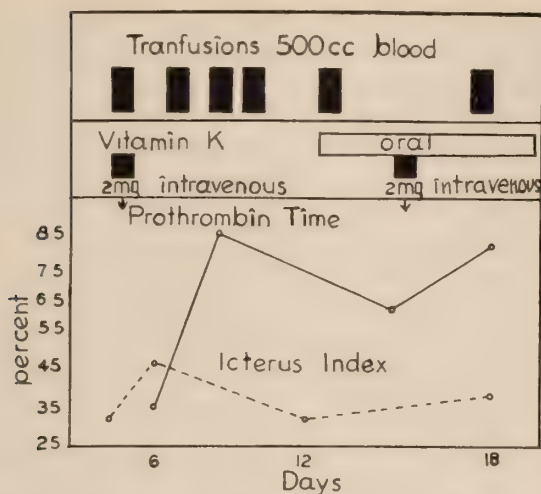


FIG. 1. Failure of prothrombin response to oral vitamin K therapy and successful prothrombin response to parenteral vitamin K. (Neoplasm of duodenum, duodeno-jejunosomy. Obstructive jaundice.)

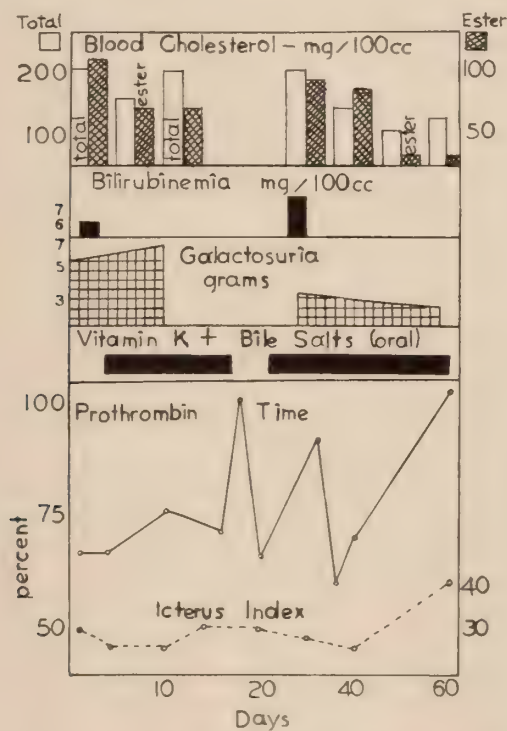


FIG. 2. Comparison of prothrombinemia and the results of different types of liver function test (case of common duct stones, intrahepatic calculi, choledochotomy, cholecystectomy).

Our observations indicate that marked impairment in liver function frequently co-exists with normal prothrombin levels in the blood and, conversely, that hypoprothrombinemia may occur when liver function is found to be normal when measured by standard tests.

The prothrombin response in patients with fluctuating degrees of liver impairment merits attention. Our observations confirm the established fact that liver impairment cannot be ruled out by a single type of liver function test. The prothrombin response to vitamin K may be normal when tests show one type of hepatic dysfunction and may be abnormal in another type of dysfunction. For example, a favorable prothrombin response to the oral administration of vitamin K was noted in a patient with obstructive jaundice due to common duct stones and intrahepatic calculi despite the fact that the galactose tolerance test was markedly positive (fig. 2). Upon cessation of vitamin K therapy, hypoprothrombinemia (62 per cent of normal) developed promptly, indicating vitamin K deficiency, although the liver was evidently still capable of utilizing vitamin K. The plasma cholesterol partition at that time was normal. Thereafter the galactose tolerance test showed improvement even though the intensity of jaundice remained unaltered. A different type of impairment of liver function was then detected by the abrupt reduction in total plasma cholesterol and ester fraction. Hypoprothrombinemia recurred despite the oral administration of vitamin K and bile salts. Later the prothrombin response to vitamin K returned to a normal level although the cholesterol ester fraction remained low. These findings suggest that an abnormal plasma cholesterol level may serve to indicate a type of liver injury which may be associated with failure to utilize vitamin K.

THE VALUE OF VITAMIN K IN CHOLEMIC AND OTHER TYPES OF BLEEDING

It has been definitely established that vitamin K has no curative effect on the bleeding tendency of hemophilia. In hemorrhagic disease of the newborn vitamin K is definitely effective (cf. Brinkhous (1), for bibliography). Cheney (12) reported benefit in the bleeding tendency of three subjects with nephritic uremia who had purpura and epistaxis. Bleeding ceased promptly after parenteral injection of vitamin K. The abnormal plasma coagulation time was reduced to less than the normal average. In one instance venous thrombosis developed. Cheney reported additional instances of subclinical K hypovitaminosis which were manifested by only slightly delayed coagulation time of the blood and plasma. The coagulation time in six presumably normal individuals was reduced to the low point of 1 or 2 minutes by the oral or parenteral administration of vitamin K. The possibility of the existence of subclinical K hypovitaminosis without demonstrable changes in prothrombin time enlarges the field of vitamin K therapy. The application of vitamin K therapy to cases of this type will be referred to again.

The value of vitamin K in the control of occult bleeding and hemoptysis. We have been unable to correlate the incidence of occult gastro-intestinal bleeding with hypoprothrombinemia. Vitamin K therapy failed to eliminate this type of bleeding. The presence of occult blood in the stool of patients with jaundice must be regarded in many instances as being unrelated to the hemorrhagic tendency of hypoprothrombinemia

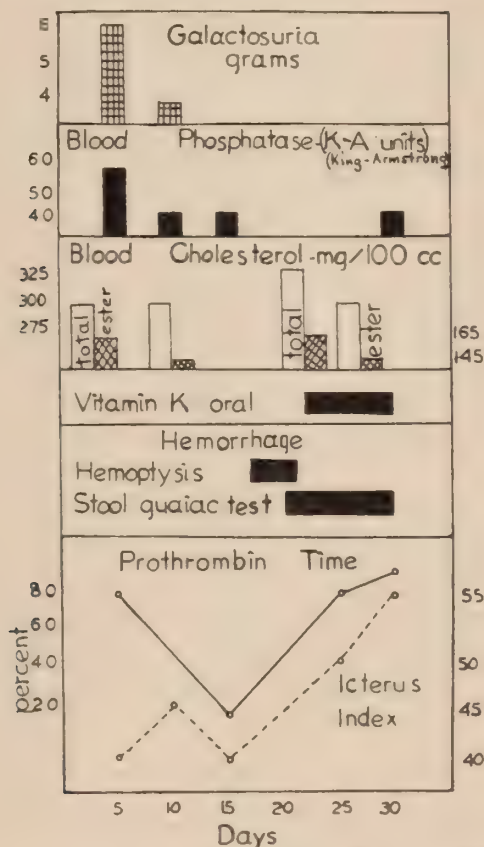


FIG. 3. The lack of correlation between incidence of occult intestinal bleeding and hemoptysis and the plasma prothrombin level. (Obstructive jaundice due to metastatic carcinoma.)

(Lichtman (13)). In patients with ulcerative colitis and associated hypoprothrombinemia, vitamin K therapy definitely failed to control occult intestinal bleeding.

In a patient whose colon had been resected for adenocarcinoma, obstructive jaundice due to periportal metastases developed. Hemoptysis also occurred which was attributed to hypoprothrombinemia; the plasma prothrombin was 18 per cent of normal. The hemoptysis, however, ceased

before correction of the plasma hypothrombinemia. Occult intestinal bleeding which developed coincidentally, was not affected by oral administration of vitamin K, although the latter promptly restored the prothrombin level to normal (fig. 3).

The value of vitamin K therapy in bleeding associated with normal prothrombin time. Two series of observations may be included under this heading. In one, a hemorrhagic tendency developed in patients whose prothrombin time was normal at the time bleeding occurred and who had been receiving oral vitamin K and bile salts. This phenomenon occurred following operations for common duct stone, acute cholecystitis and liver abscess. The bleeding tendency manifested itself by oozing from the wound. In one instance following laparotomy for common duct stone a massive internal hemorrhage occurred with a sudden drop in hemoglobin. The patient made an uneventful recovery. This type of bleeding, therefore, occurred independently of prothrombin deficiency and in spite of vitamin K therapy.

In another small group of cases of patients with normal prothrombin time it was our impression that the intravenous administration of vitamin K promptly relieved spontaneous bleeding from surgical wounds. One instance of this type of hemostasis was encountered in a patient with a fecal fistula which followed resection of the colon for ulcerative colitis. In another patient, postoperative oozing of blood from the wound followed drainage of a liver abscess; the bleeding stopped after a single intravenous injection of vitamin K. Such evidence, although far from conclusive, warrants the further extension of vitamin K therapy irrespective of the prothrombin level of the circulating blood. Weir, Butt and Snell (9) cite a similar observation in a jaundiced subject with probable stricture of the common bile duct who had received vitamin K pre-operatively. Capillary oozing, noted at the operating table, was promptly controlled by intravenous vitamin K.

SUMMARY

The value of vitamin K in the prevention and relief of bleeding due to hypothrombinemia is now definitely established.

Vitamin K will not correct hypoprothrombinemia if it fails to reach, or be utilized by, the liver. The parenteral administration of vitamin K makes vitamin K available to the liver, but does not necessarily assure its utilization by this organ.

In hypoprothrombinemia due to faulty utilization of vitamin K by the liver, special attention must be paid to the treatment of the underlying liver damage as well as to the deficiency of vitamin K. The plasma prothrombin response to vitamin K depends upon an intrinsic function of the liver which may or may not be correlated with the results of standard liver function tests.

The correction of hypoprothrombinemia fails to benefit in some instances of bleeding assumed to have resulted from it. Bleeding of the types such as occult intestinal hemorrhage or hemoptysis, attributed to hypoprothrombinemia is not always benefited by the correction of the prothrombin deficiency. On the other hand, there is evidence favoring vitamin K control of postoperative and other types of bleeding in patients with normal plasma prothrombin values.

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A CASE OF XANTHINE CALCULI¹

A. HYMAN, M.D., AND H. E. LEITER, M.D.

Xanthine calculosis in the urinary tract is of such rarity that its occurrence at this hospital merits publication. From the clinical urological standpoint, these calculi differ in no way from other types of urinary calculi. They are, however, of considerable physiological and chemical interest because they represent a disturbance of protein metabolism and are thus allied to uric acid and cystine calculosis.

The following is the eighteenth case in the literature of xanthine stone in the urinary tract.

CASE REPORT

History. (Adm. 441887.) A. K., a married woman, 27 years of age, was first seen on November 30, 1938, because of pyuria and recurrent episodes of pyelonephritis. The first attack occurred twelve days after an appendectomy in 1928. In December, 1932, she had another episode of left pyelonephritis which kept her in bed for one week. In 1933, she again had pyelonephritis and in 1936 she passed some urinary gravel. In October, 1938, following an upper respiratory infection, she developed left lumbar pain and a temperature of 103°F. Since that time she has been running a low grade fever associated with persistent pyuria with staphylococcus aureus and colon bacilli in the urine culture. This pyuria failed to respond to mandelic acid and sulfanilamide therapy.

Examination. The patient was obese with some evidences of hypopituitarism and hypothyroidism. There were no other abnormalities aside from a mild left lumbar tenderness.

A plain roentgenogram of the urinary tract disclosed the presence of a stone the size of an olive in the lower pole of the left kidney and a smaller calculus in the region of the middle calyx. Excretory urograms revealed a normal right kidney pelvis and ureter. The left kidney showed good excretion with the stones in the lower and middle calyces.

Course. She was admitted to The Mount Sinai Hospital and on December 9, 1938, the left renal calculi were removed through two nephrotomy incisions. Her postoperative course was rather stormy at first but after a few days was uneventful. The calculi were composed of ammonium magnesium phosphates.

On June 10, 1939, she was readmitted to this hospital with a temperature of 104°F., nausea and persistent vomiting, right lumbar pain and a blood urea nitrogen of 77 mg. per cent. Cystoscopic examination disclosed a retention of 40 cc. of thick milky urine within the right kidney. A large catheter was left indwelling in the right renal pelvis. Following a transfusion and large amounts of intravenous fluids, her condition improved rapidly and the blood urea nitrogen came down to 17 mg. per cent. A plain roentgenogram of the urinary tract at this time showed a few small con-

¹ Read before the monthly Urologic Conference of Dr. A. Hyman, The Mount Sinai Hospital, March, 1940.

cretions in the lower pole of the left kidney and a small shadow in the region of the right kidney.

On January 27, 1940, the patient reported that she had been well until one week before when she developed pain in her right lumbar region. This was followed by fever and pyuria. A flat plate of the urinary tract was taken and revealed the presence of two calculi in the lower end of the right ureter, each $1\frac{1}{4}$ by $\frac{3}{4}$ centimeter. Excretory urography disclosed a mild dilatation of the right renal pelvis and ureter above the stones.

The patient was readmitted to the hospital on February 1, 1940. The day before admission she passed one calculus which was yellowish in appearance and immediately suggested an organic type of stone. She was cystoscoped and a number 5 ureter catheter was made indwelling in the right ureter for ninety-six hours. After removal of the catheter and the administration of one ampoule of prostigmin 1:2000



FIG. 1. Intravenous pyelogram showing the presence of two calculi in the lower end of the right ureter

every two hours for three doses, the patient passed the second calculus. These calculi were smooth and yellowish in color, and on chemical examination by Miss Miriam Reiner were found to consist of pure xanthine with a small trace of calcium.²

DISCUSSION

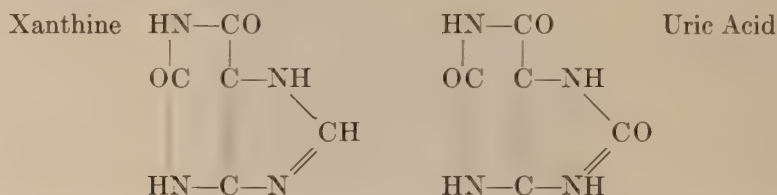
Biochemistry. Uric acid is excreted by molluses, arthropods and insects. In fishes and amphibia, its place is taken by urea. In reptiles and birds, uric acid is again the predominant excretory product of protein metabolism and in mammals with rare exceptions (Dalmatian dog) urea again is the chief waste product (1).

The purines in man are both exogenous and endogenous in origin.

² The unusual nature of the stones was recognized by Miriam Reiner, M.Sc., whose kind cooperation we wish to acknowledge.

The latter is derived from the breaking down of nuclein and nucleic acid. The former is derived from foods which have a large amount of nucleoproteins such as meat, liver, sweetbreads, kidney. Another source of exogenous purine are the methylpurines which are found in coffee, tea, cocoa and which in their passage through the body lose the methyl radical and are eliminated as xanthine and hypoxanthine. In the metabolism of nucleic acid the latter is first broken into two dinucleotides containing purine and pyrimidine by an enzyme tetranuclease. The purine nucleotides are then converted into the nucleosides adenosine and guanosine which, after action by special enzymes are then changed to adenine and guanine.

By deaminization, the four substances, adenine, guanine, adenosine and guanosine are changed into hydroxypurines. Thus, hypoxanthine is monohydroxypurine; xanthine is dihydroxypurine and uric acid is trihydroxypurine. Hypoxanthine and xanthine are in part converted by oxidation into uric acid. Jones (2) reports that in man, the liver is the only organ from which an enzyme can be obtained capable of oxidizing xanthine to uric acid. Thus, the liver is the most probable site of uric acid formation in man. The following chemical formulas show how closely xanthine and uric acid are allied.



It has been stated that 90 per cent of the purine nitrogen in the urine is in the form of uric acid and 8 per cent is made up by the purine bases. Thus, with an estimated daily output of 0.4 to 1 per cent uric acid, the purine bases would amount to one tenth of this quantity (3).

The first xanthine stone was described by Marcet (4) in 1817. This calculus was subjected to a number of chemical analyses in the succeeding thirty years. In 1937, Kretschmer (5) wrote an excellent paper on this subject, summarized the reports in the literature and reported the case of a man with a large xanthine vesical calculus which was removed by litholapaxy.

Since then, Ratner and Strasberg (6) reported another case in a woman who passed two calculi, each 2 by 1½ centimeters, and which were composed of xanthine 60 per cent, uric acid 30 per cent and calcium oxalate 10 per cent. We take the liberty of emphasizing a few of the features brought out in the study of sixteen cases by Kretschmer.

Physical Characteristics. The color varies from canary yellow to light or dark brown; they are smooth, waxy, shiny if rubbed with a cloth and

rather hard. In the cases of Kretschmer, Ratner and Strasberg and in our case the roentgenogram revealed a shadow cast by the xanthine stone. In Ratner's patient the opacity to the x-rays was attributed by the authors to the presence of 10 per cent calcium oxalate.

Any stone containing 90 to 95 per cent of any one salt is considered a pure stone in practice. Aschner's case had two distinct kinds of stones, the smaller ones were pure xanthine (99.2 per cent), while the larger ones showed the presence of calcium phosphate, 69.4 per cent; calcium oxalate, 30.5 per cent; and xanthine, 0.1 per cent. In Israel's case of bilateral calculi, the right-sided stones were pure xanthine with traces of phosphates and carbonates while the stones on the left side were composed of uric acid. The stone in White's case was composed of xanthine and cystine with an outer layer of triple phosphates. Cystine calculi were removed from the opposite kidney a few months later.

Of the 16 cases, 8 were in the bladder, 3 were in the kidney and in 4 cases the site was not mentioned. The youngest patient was 4 years of age and the oldest was 69 years. The greatest incidence was between the ages of 4 and 15 years. Male patients predominated. The largest stone was 2 inches in diameter and weighed 350 grams. In 11 cases the stone was single; in 3, they were multiple; and in 2 cases there was no mention of this point.

A review of the literature discloses only a few instances of passage of stones which under ordinary circumstances would appear too large to pass spontaneously from the ureter as in our case and that of Ratner and Strasberg (6). Perhaps this is made possible by the fact that these stones are smooth.

Treatment. The problems of therapy in cases of xanthine calculi are identical with those applied to any other stones in the urinary tract. From the standpoint of prevention of recurrence, it would appear that the following regime seems indicated. There should be a large fluid intake so that the urine has a low specific gravity. The diet should be mixed with a preponderance of vegetables, fat, carbohydrates with a low purine intake. Liver, brain, sweetbreads, kidney, roe, meat extract, coffee, tea, alcohol, cocoa, chocolate and asparagus should be avoided.

Excessive intake of salt, salt meat and fish are likewise to be restricted because uric acid precipitates more readily in an abundantly salty urine.

SUMMARY

1. A case of xanthine calculi in the urinary tract is reported.³ This is the eighteenth case in the literature.

2. Some interesting features of the biochemistry of the purines and of cases of xanthine calculi reported in the literature are reviewed.

³ Since this paper has been submitted for publication, the patient passed a small calculus, which on examination was found to be composed of cystine.

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SPONTANEOUS PNEUMOTHORAX SIMULATING ACUTE CORONARY OCCLUSION

ARTHUR M. MASTER, M.D., HENRY H. KALTER, M.D., AND
SIMON DACK, M.D.

[From the Cardiographic Laboratory, and the Medical Service of Dr. George Baehr]

A survey of the literature of pneumothorax reveals but few reports of electrocardiographic changes in this condition. In 1913, Egan (1) studied two cases of artificial pneumothorax and noted P-wave changes, alterations of the voltage of the QRS complexes and axis deviation. Another investigator, Rehberg (2), found an increase in the size of the P-waves and a decrease in the amplitude of the T-waves in artificial pneumothorax. He attributed these changes to vagus stimulation. Ontaneda, Mazzei and Pasqualini (3) reported two cases of spontaneous pneumothorax, the onset of which simulated the syndrome of angina pectoris. The electrocardiograms showed lowering of the T-waves. More extensive electrocardiographic changes in the standard leads in spontaneous pneumothorax were reported by Master (4). These changes consisted of left or right or unusual axis deviation, low voltage of the QRS complex, depression or elevation of the RS-T transition, and flattening or inversion of the T-waves. They were attributed to rotation and displacement of the heart. Master emphasized that the electrocardiogram may resemble that obtained in myocardial damage and even in coronary occlusion. More recently, Master and his associates (5) reported several other cases of pneumothorax with abnormalities in the precordial lead consisting of inversion of the T-wave and a very small or absent initial positive deflection. These changes resembled those seen in myocardial infarction. The standard and the precordial leads in these cases became normal after reexpansion of the lung. These observations are of significance because in patients of middle age with spontaneous pneumothorax the clinical picture may often simulate that of coronary occlusion. The occurrence of severe chest pain and the presence of suggestive electrocardiographic abnormalities may thus lead to an erroneous diagnosis. The following case emphasizes this point.

CASE REPORT

History. (Adm. 372886.) A. L., a man, 50 years of age, was suddenly seized, while dressing, with extremely severe squeezing pain in the left anterior chest, radiating down to the left elbow. He was told that he had suffered a "heart attack" and was, therefore, referred to the hospital two days later on October 30, 1934. The severe pain had persisted for two days.

Examination. The patient was a thin, rather well developed man, who complained of a tight feeling in the left chest. Slight cyanosis of the lips was present. The heart was not enlarged; the apical impulse was felt just within the left nipple. The heart sounds were distant and there were no murmurs. The rhythm was regular, the rate was 100 per minute, and the blood pressure was 120 systolic and 70 diastolic. The radial arteries were moderately sclerotic. The left chest was hyperresonant, and the breath sounds were diminished to absent. Vocal fremitus over the left chest was also absent. The right chest was normal. These signs were attributed to spontaneous left pneumothorax with collapse of the left lung.

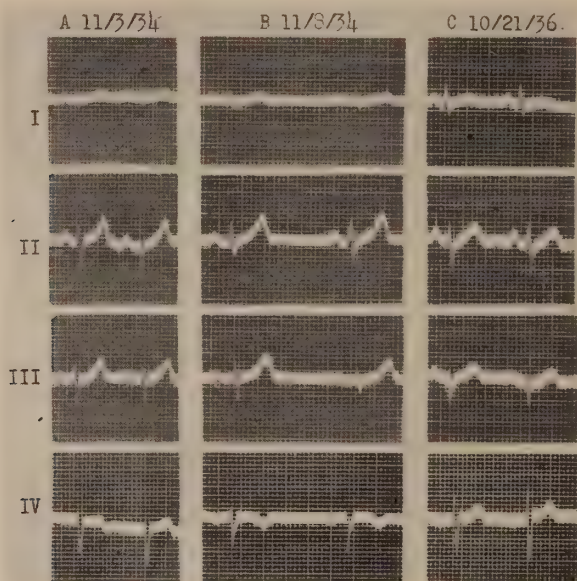


FIG. 1. A. November 3, 1934, five days after onset of pneumothorax. Electrocardiogram reveals an unusual axis deviation (low R-I and deep S-2 and S-3). The R-4 is very small, varying from 0 to $\frac{1}{2}$ mm. T-4 is biphasic.

B. November 8, 1934. Sinus bradycardia rate 58. The QRS voltage is lower, R-4 is unchanged, and T-4 is inverted.

C. October 21, 1936. Follow-up record. Lung completely reexpanded. The electrical axis is more normal. Lead IV is now entirely normal; R-4 is of normal amplitude and T-4 is upright.

Course. A slight leucocytosis of 12,300 was present, with 58 per cent polymorphonuclear leucocytes. The sedimentation rate was normal ($1\frac{1}{2}$ hours). The temperature rose on the second and third day to 102.4°F ., and returned to normal levels on the fourth day of admission. The blood pressure dropped to 80 systolic and 58 diastolic on the third day. Subsequent readings were normal. The venous pressure measured 4 cm., with no rise on right upper quadrant pressure, and the saccharin circulation time was 15 seconds. These were normal readings. On November 2, x-ray examination revealed a left pneumothorax with 50 per cent collapse of the left lung. On discharge on December 4, the left lung had completely reexpanded. Some chest discomfort persisted for about a month despite definite objective improvement.

The electrocardiogram taken on November 3 (Fig. 1A), five days after the onset of his illness, showed a regular sinus rhythm, rate 95 to 100 per minute. There was an unusual axis deviation, the QRS complex in lead I being of very low amplitude

and slurred, and a deep S-wave being present in leads II and III. The initial positive deflection in the precordial lead (R-4) varied from absent to $\frac{1}{2}$ mm. The T-wave was diphasic in lead IV. On November 8 (Fig. 1B) the heart rate was 58 to 65, and T-4 had become completely inverted. A check-up examination in October, 1936, two years later (Fig. 1C) revealed that the electrocardiogram, including the precordial lead, had become entirely normal.

COMMENT

The case presented is that of a patient in the coronary age group, who suffered an acute attack of severe squeezing precordial pain, radiating down the left arm. The patient was referred to the hospital with the diagnosis of acute coronary occlusion. The electrocardiogram showed a pattern suggestive of myocardial infarction. The transient fall in blood pressure, slight leucocytosis and fever also pointed to such a diagnosis. However, the physical and x-ray findings were those of a spontaneous left pneumothorax.

The most striking electrocardiographic changes in this case, as in the ones previously reported (5), appeared in the precordial lead, and consisted of absence of the initial positive deflection (presence of a deep Q-4) and inversion of the T-4. Such a pattern is characteristic of infarction of the anterior surface of the left ventricle. In this case, however, myocardial infarction was not present. All the symptoms and signs could be attributed to the left pneumothorax, and all the abnormalities disappeared with reexpansion of the lung. Undoubtedly, the electrocardiographic changes were associated with rotation and displacement of the heart, which has been shown to have a marked effect on the electrocardiogram (6).

This case demonstrates that in spontaneous pneumothorax, not only the character and location of the pain, but also the electrocardiographic changes produced by the cardiac rotation or displacement, may be undistinguishable from the pain and electrocardiographic abnormalities observed in acute coronary occlusion.

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CYSTIC TUMOR OF THE FOURTH VENTRICLE

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[From the Neurological and Neurosurgical Services and The Division of Laboratories]

In a recent review of brain tumors in children (to be published), comprising the neuropathological and neurosurgical collection at The Mount Sinai Hospital, eight out of fifteen surviving cases were instances of pial (i.e., vascular) malformations, infratentorial in location. They had been variously labelled as: vascular malformation with secondary glial reaction, hemangio-endothelioma, hemangioma, and hemangiomatous meningeoma, terms indicating various expressions of a basically similar condition. Out of seven cases with a five year survival period, five belonged to this group of vascular malformations. There was only one such case in the list of fatalities. Thus, it may be assumed that these tumors offer the best opportunity for successful surgical intervention.

The following case is a recent addition to this group. It is a rather unusual type of vascular malformation and, in addition, it was found in an unusual anatomical position. But, most important of all, is the complete and maintained postoperative recovery of the patient.

CASE REPORT

History. (Adm. 430195.) A boy, 13 years of age, entered the Neurological Service of Dr. Israel S. Wechsler on September 29, 1938. His illness had begun early in 1936 with periods of dull pain at the back of his head and neck following exertion. Soon thereafter, persistent early morning vomiting set in often associated with occipital pain. In the course of a year, he became too weak to attend school although he still maintained some out-of-doors activity. Five months before admission he began to experience peculiar episodes of "smeared" vision, occurring once a week and lasting about an hour. Then he began to suffer from intermittent attacks of pain over his left eye. The pain recurred at intervals of several days, lasting a few hours each time and vanishing without medication. Next he noticed that he would become dizzy while playing. In addition, dizziness and an "uncomfortable feeling" would occur if he would lie flat on his back. He had learned that he could avoid these sensations and the occipital pain, whether in motion or at rest, by bending his head slightly forward and tilting it to the right side, and holding it fixed in the resulting position. To this end he would sleep with his head propped up on two pillows. During the year preceding admission, he had lost twelve pounds in weight.

Examination. The boy was thin and poorly developed. When walking or lying he held his head in a fixed position, bent slightly forward with the chin turned to the left side. If he turned to the left or right side while walking, he would become

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dizzy. With his eyes closed he tended to veer to the right. When his head was tilted backwards he experienced the "uncomfortable feeling" which he said was not dizziness but which he could not characterize more precisely. With his head in this position, whether he was erect or lying flat on his back, a coarse nystagmus to the right side would appear. His fundi showed early bilateral papilledema. The corneal reflex was absent on the right side and diminished on the left. His hands and feet, when extended, displayed coarse, rapid tremors. The deep tendon reflexes were hyperactive. His blood pressure was 115 systolic and 80 diastolic. There was a yellow, strawberry-like patch in the skin behind his left ear.

Laboratory Data. Cerebrospinal fluid: clear and colorless; initial pressure, 320 mm. of water; Ayala index, 5; cells, 0; Pandy test, 4 plus; total protein, 92 mg. per cent. The Wassermann reaction was negative in the blood and the cerebrospinal fluid.

Course. The diagnosis of an infratentorial neoplasm, probably intraventricular in location, was made. On subsequent examination, localized tenderness was found over the second cervical vertebra. It was then felt that the tumor probably extended below the foramen magnum. Bilateral trephine operations and ventricular punctures, performed by Dr. Sidney Gross (service of Dr. Ira Cohen) one week after the

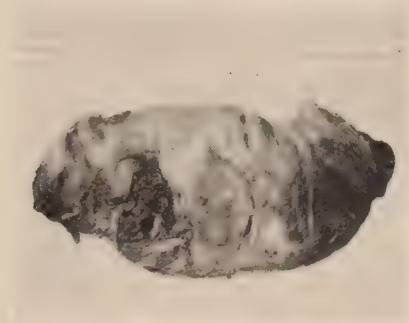


FIG. 1. The cyst as removed at operation

patient's admission, disclosed an internal hydrocephalus and the patient was immediately subjected to a suboccipital craniotomy. An elliptical-shaped cyst, measuring $9\frac{1}{2}$ by 6 by 6 cm. and containing clear, yellowish fluid, was found in an enlarged fourth ventricle. At its upper pole the cyst separated the lobes of the cerebellum and was invested by a "thin arachnoidal-like membrane." From the undersurface of its body delicate fibers, described as resembling a spider web, extended to the floor of the ventricle. The lower pole of the mass, less firmly attached than the upper, extended into the spinal canal. The mass appeared to be well-encapsulated and was readily removed *in toto* by blunt dissection (fig. 1).

Surgical Pathology. (Surg. 64280.) The mass on closer examination appeared to be composed of a smooth glistening transparent membrane applied to a somewhat fleshy substance. On sectioning this was found to be a wall about 7 mm. thick. The inner surface presented a glistening, irregular, wrinkled appearance.

The microscopic findings reported by Dr. J. H. Globus read as follows: "Cross-sections of numerous areas of the cyst wall were stained with the various histological techniques. One region, which is somewhat thicker than the other areas examined, discloses the essential features of the cyst wall (fig. 2A). There is an outer zone composed of intertwining bundles of collagenous fibers and an inner zone consisting of clusters of irregularly shaped endothelial-lined channels, usually containing blood

cells. Between these two zones there is a narrow region of transition as the collagenous elements diminish in number and the vascular elements increase. In the inner zone many of the vessels are encircled by areas of fibrosis and hyalinization. In the transitional region there are vessels and connective tissue fibers partially or completely calcified (fig. 2B). Near some of them there are small sheets of epithelial cells, probably ependymal (fig. 2C). Throughout the more vascular zone, but particularly in the transitional area, there are numerous pigment-laden cells, evidence of previous extravasations of red blood cells. Scarlet Red preparations display occasional aggregates of fat-laden phagocytes. In the more vascular layer, isolated collagenous bundles, cut in cross-section and displaying round to pyriform outlines,

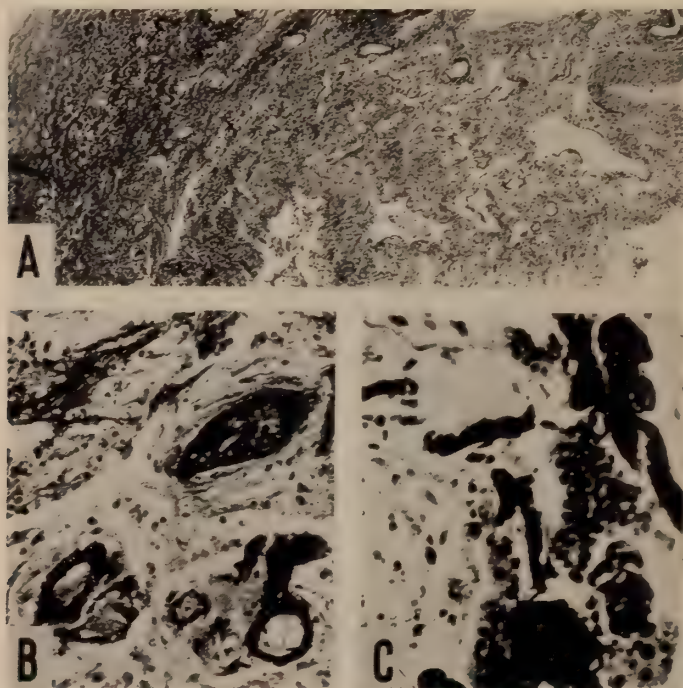


FIG. 2A. A cross-section of the cyst wall showing the dense collagenous zone on the left and a wider hemangiomatous zone to the right (hematoxylin-eosin, photomicrograph, 30 \times).

FIG. 2B. An area in the hemangiomatous zone showing calcification of blood vessels and calcification of connective tissue fibers (hematoxylin-eosin, photomicrograph, 310 \times).

FIG. 2C. Groups of epithelial cells in the tumor (probably ependymal) in the proximity of areas of calcification (hematoxylin-eosin, photomicrograph, 475 \times).

resembled abnormal cell forms. In hematoxylin-eosin and Mallory preparations the central mass of these bundles stains poorly or not at all. However, the Mallory stain discloses a narrow band of connective tissue enclosing each of these "bodies" and their true character becomes apparent. Silver and gold preparations bring out the vascular pattern and the meshwork of connective fibrils throughout the tissue. The diagnosis is *cystic hemangiomatous meningeoma*, arising probably from the meninges in the roof of the posterior part of the fourth ventricle. The presence of ependymal cells would indicate that the *tela choroidea* of this region contributed to some extent in the development of the cyst."

Postoperative Course. Re-examination of the patient several days after operation

showed slight blurring of the nasal margin of the left disc, a coarse rolling nystagmus to the left and right sides, a mild generalized hypotonia, and depressed but equal deep tendon reflexes. For one week postoperatively the patient's temperature was somewhat elevated (101°F. to 103°F.). Then over a period of several days, it fell gradually to normal. But, after one day, a spiking temperature set in with a daily rise to 103°F. (usually in the morning). This persisted for the next seven weeks. Although his pulse rate varied considerably (90 to 120 per minute, occasionally to 140 per minute), these changes did not synchronize with the changes in temperature. His respiratory rate during this period remained within normal limits. The temperature elevation was accompanied by no subjective complaints and there were no laboratory or physical findings to account for it.

Six weeks after operation a physical examination disclosed some of the signs found on admission but they were now diminished in intensity. He was tense and would not walk freely, but his gait was only slightly unsteady and he had no difficulty in turning. There was some posturing of the head to the right but no stiffness of the neck. The nasal margin of the left disc still showed a slight blurring. The nystagmus, coarse and rolling, occurred only on right lateral gaze. The upper and lower extremities displayed tremors only occasionally on extension. There was also a slight ataxia, more marked on the right side. All the deep tendon reflexes were hyperactive.

Two weeks later, eight weeks after operation, the patient began to experience severe headache and vomiting and for the first time exhibited subjective signs of fever. There was some bulging of the operative decompression and some tenderness over the upper cervical spine. The fundi were normal. There was practically no ataxia. Otherwise the physical findings were the same as at the previous examination. The blood showed a leucocytosis of 20,000 cells per cubic millimeter of which 85 per cent were segmented polymorphonuclear neutrophils. On the following day an aspiration of the decompression bulge was performed and about 75 cc. of clear, colorless fluid was removed. The fluid contained 67 white blood cells per cubic millimeter of which 60 per cent were mononuclear cells. A culture of the fluid proved the latter to be sterile. Within two days after this aspiration the patient's temperature dropped to normal and has remained so to date. The patient was discharged from the hospital on December 15, 1938, ten weeks after operation.

Follow-Up. For the next two months he was subjected to x-ray therapy as a prophylactic measure. This was given in four cerebellar fields and reached a maximum of 1200 gamma in the last treatments.

He returned to school and after several months was reported as "engaging in all normal activities." When last examined in the Follow-Up Clinic, March 5, 1940, he was asymptomatic and the neurological examination was reported as entirely normal.

SUMMARY

A case of a fourth ventricle tumor in a boy, thirteen years of age, is presented. The tumor, a cystic hemangiomatous meningeoma, was successfully removed at operation. The postoperative course was complicated by fever of unknown origin for eight weeks, which subsided following aspiration of the operative site and removal of sterile fluid. The patient is apparently completely cured. The case, a type of vascular malformation, is one of a group which offers the best opportunity for successful surgical intervention. Statistics supporting this view are also presented.

We wish to express to Dr. J. H. Globus our appreciation for his supervision and help in the study and presentation of this case.

OTOGENOUS TETANUS

SAMUEL ROSEN, M.D.

[From the Medical Service of Dr. G. Baehr and the Otological Service of Dr. J. Maybaum]

Most cases of otogenous tetanus reported in the literature are associated with injury or a foreign body. Inasmuch as most of the cases reported in the literature are by foreign authors, it would seem that this disease is either rare in America or it has been overlooked.

CASE REPORT

History. (Adm. 453277.) H. C., a male Negro, 18 years of age, walked into the hospital on the morning of December 23, 1939. For the past two years his right ear had been discharging; at times the discharge had been foul. Four days before admission the patient noticed that his right upper lid was drooping and that he had some pain in the right side of his face on chewing.

Examination. The right ear showed a large central perforation through which a mass of red swollen mucosa of the inner tympanic wall protruded. The discharge was mucopurulent and moderate in amount. The hammer handle was visible. No mastoid tenderness was present. The patient heard a moderately soft whisper. There was some right facial weakness. The temperature, pulse and respirations were normal. The general physical examination was negative.

The combination of chronic purulent otitis media of two years' duration with the onset of facial weakness and pain on chewing usually is an indication for radical mastoidectomy.

The patient could open his mouth to the limit but on so doing complained of a "tightness" in the region of the right jaw joint. No satisfactory explanation could be found for this. The following morning the picture was essentially the same except the facial weakness was more marked and the patient could not completely open his mouth. The blood count was normal and the Wassermann reaction was negative. The inability to open his mouth completely was impressive and, on searching the literature, it was found that tetanus seemed to be the diagnosis which seemed most applicable. The following morning the patient was found in opisthotonus; with a rigid neck, a cement-like rigidity of the abdomen, some rigidity of the upper and lower extremities and trismus was now almost complete.

Course. The patient was transferred to the medical service at once for tetanus therapy. He developed generalized tetanic convulsions precipitated by noise or movement. Avertin, amytal and ether were necessary to relax the patient. Stridor and laryngeal spasm necessitated tracheotomy. The cerebrospinal fluid was negative. The temperature rose to 104°F. and the respiratory rate rose to 50 per minute. Signs of bilateral lower lobar pneumonia appeared. One hundred thousand units of tetanus antitoxin were given intravenously for two days then 50,000 units for several days thereafter. This was later reduced to 20,000, 10,000 and finally 5,000 units every three days. Altogether 795,000 units of antitoxin were given within four weeks. The course of the pneumonia was very severe. At the end of two weeks the temperature became normal and the tetanic spasms had almost entirely disappeared.

The right ear continued to discharge. The perforation became larger. Cultures of the discharge taken from the right ear showed *Clostridium tetani* (tetanus bacillus) and *Proteus* bacillus. This was proven by the inoculation of mice and guinea pigs. The animals inoculated with cultures died soon after and tetanus bacilli were recovered. The animals inoculated with cultures plus tetanus antitoxin survived.

It was felt that the tetanus focus in the ear should be eradicated as far as possible. A thorough mastoidectomy was, therefore, done. The mastoid bone was diploeic, soft and cut easily. The posterior canal wall was taken down, the aditus opened widely and the ossicles could then be seen. They appeared normal. Cultures of the bone at operation were negative. At this point, when a modified radical mastoidectomy had been done, the patient went into shock. The operation was, therefore, stopped. It was decided later not to complete the radical procedure but to observe the patient in the Out-Patient Department. The culture taken just before the operation, the specimen taken at the operation and those cultures taken since the operation have all been negative for tetanus. The patient is well.

COMMENT

The case herein reported is one of generalized tetanus complicating a chronic purulent otitis media with recovery of tetanus bacilli from the middle ear indicating that the middle ear may be the focus of a generalized tetanus.

EARLY DIAGNOSIS OF OTITIC MENINGITIS IN CHILDREN¹

SAMUEL M. BLOOM, M.D.

[From the Otological Service of Dr. J. L. Maybaum]

The advent of chemotherapy for meningitis of otitic origin has brought a dramatic change in the prognosis of this heretofore dreaded complication. However, the use of sulfanilamide and its derivatives has also introduced many problems, chief of which has been the obscuring of familiar signs and symptoms accompanying otogenous infections. It is for this reason that it is desirable to direct attention to the early diagnosis of otitic meningitis in children.

CASE REPORTS

Case 1. History. (Adm. 432686.) A three and one-half month old male infant had an upper respiratory infection and a discharging right ear for two weeks. Three days before admission he developed a temperature of 103°F., and indicated pain in the ear by pulling at it.

Examination. There was evidence of acute mastoiditis with subperiosteal abscess. There were no neurological signs. A simple mastoidectomy was performed and a thoroughly broken down infantile mastoid was found. There were no exposures of dura or lateral sinus. The following day, the temperature rose to 105°F., the baby appeared restless, but there were no physical signs to account for the temperature. On the second postoperative day, the temperature remained elevated. The infant continued to be restless, and frequently worked his dressing off by rolling his head. The only positive finding was a full anterior fontanel. There was no definite stiff neck, nor were there positive Kernig or Brudzinski signs. The respirations were rapid, and there was a slight grunt. A roentgenogram of the chest was negative. There had been no vomiting or convulsions. However, because of the restlessness and full fontanel, a lumbar puncture was performed. The cerebrospinal fluid was cloudy, contained 1,260 cells per cubic millimeter, of which 90 per cent were polymorphonuclear leucocytes; the Pandy reaction was 4 plus; and Gram-positive cocci in chains were seen on smear. Sulfanilamide was administered. The following day the blood and cerebrospinal fluid were reported as showing *Pneumococcus*, type V on culture. Accordingly, sulfapyridine was substituted for the sulfanilamide. In addition, *Pneumococcus*, type V antiserum was administered intravenously (20,000 units daily), and intrathecally (1,500 units daily, with human complement).

The patient seemed to improve after a week, but then relapsed; the temperature ranged to 103°F., and the cerebrospinal fluid cultures remained strongly positive. A right external rectus paresis developed. Because of spinal arachnoid block, a ventricular puncture was performed. This revealed yellow turbid fluid, loaded with Gram-positive diplococci. The baby's condition was too poor to permit further surgery, and the patient died. Autopsy permission could not be obtained.

¹ Read at the conference of the Otological Service of The Mount Sinai Hospital, March 13, 1940.

Case 2. History. (Adm. 436212.) A five year old boy was admitted to the hospital because of fever and pain in the left ear for three days. He had had a cough for ten days. A tonsillectomy and adenoidectomy had been performed at another institution six months before because of frequent colds.

Examination. The child appeared to be acutely ill. He was coughing, and had a temperature of 102.4°F. The left ear presented a full reddened drum, covered with hemorrhagic blebs, obscuring all landmarks. There was a thin pulsating discharge from an antero-inferior perforation. There were no canal wall changes or mastoid tenderness. Examination of the chest showed dullness over the left base, with bronchovesicular breath sounds, and occasional râles. The neurological status was normal. A roentgenogram of the chest confirmed the findings of a bronchopneumonia of the left lower lobe. Sulfanilamide in a dosage of 45 grains per twenty-four hours was administered.

The following day, the temperature rose to 105°F. The patient seemed to be somewhat dazed, and appeared to be guarding his neck when he sat up in bed. A lumbar puncture was suggested, but since there were no definite neurological signs, it was postponed. Twenty-four hours later (on the fifth day of otitic infection), the temperature was still elevated, and a definite stiff neck and Brudzinski sign were elicited. A lumbar puncture showed cloudy cerebrospinal fluid at an initial pressure of 110 mm. of water, 223 cells per cubic millimeter, of which 92 per cent were polymorphonuclear leucocytes, but no organisms were seen on smear. The culture of this specimen was later reported as sterile; the blood culture was also sterile.

The dosage of sulfanilamide was immediately increased to 90 grains per day. The following day the condition of the patient was much improved, and the neurological signs had abated. The patient became alert, active, and sat up in bed. A lumbar puncture now showed 140 cells, 70 per cent polymorphonuclear leucocytes, and culture of the cerebrospinal fluid showed a beta hemolytic streptococcus.

In spite of continued administration of sulfanilamide, the otitic process continued, and evidence of mastoiditis (unresolved middle ear, moderate amount of reappearing discharge, mastoid tenderness, and clouding of the mastoid cells with decalcification of the intercellular septa on x-ray examination) appeared, and a simple mastoidectomy was performed. There was pus under pressure, and considerable breaking-down throughout the mastoid. The middle fossa dura was exposed, and showed only a mild congestion.

After the operation there was a moderate febrile reaction which subsided after three days. Sulfanilamide was continued for fifteen days. The cerebrospinal fluid findings returned to normal.

Sulfanilamide concentrations in the blood varied from 6.0 to 10.1 mg. per cent; in the cerebrospinal fluid, from 6.6 to 8.2 mg. per cent; in the bony fragments, 7.0 mg. per 100 Grams. Culture of the pus from the mastoid grew beta hemolytic streptococci. After a period of five weeks' convalescence on the ward the patient was discharged improved.

COMMENT

In the first case, meningitis was suspected on the grounds of a high fever, restlessness and fullness of the anterior fontanel two days post-mastoidectomy. There were no abnormal neurological signs, and no vomiting or convulsions. To further obscure the diagnosis, the respirations were rapid and grunting.

The fatal outcome was probably due to a sinus thrombosis and extension of the suppuration from the petrous pyramid to the brain. The poor

general condition, and the age of the patient prevented adequate surgical intervention.

In the second case meningitis developed while the patient was receiving sulfanilamide for acute purulent otitis media. The meningitis was manifested only by a voluntary spasticity of the neck, and a somewhat dazed behavior. There were no neurological signs for twenty-four hours. After a lumbar puncture showed a pleocytosis, the dosage of sulfanilamide was doubled, and the meningitis subsided. In spite of the continued administration of sulfanilamide and the apparent recovery, acute mastoiditis developed, necessitating the performance of a simple mastoidectomy.

When sulfanilamide is given in acute otitis media, the patient often appears toxic, and complains of headache. While these symptoms are attributed to the drug, meningitis should be borne in mind, and a lumbar puncture should be done early to establish or rule out the diagnosis. Thus, the chemotherapy can be adequately administered, and the focus attacked by surgical means earlier than if meningitis does not complicate the picture. The oft-repeated statement that a lumbar puncture may predispose to the development of meningitis is unfounded. A lumbar puncture should be performed early on the slightest suspicion; and should not be withheld until the picture is full-blown.

TRANSIENT GLOBAL APHASIA AND HALLUCINATORY EPISODE IN NEUROSYPHILIS¹

DANIEL STATS, M.D.

[From the Neurological Service of Dr. I. S. Wechsler]

This case of neurosyphilis seems worthy of record because of a transient widespread disturbance in the higher cerebral functions in an individual who is intelligent and observant enough to give a comprehensive and accurate account of his difficulties. Another feature of special significance is a brief hallucinatory episode and a remarkable alteration in music appreciation.

CASE REPORT

History (Adm. 434764). The patient, a 43 year old Latvian-born house superintendent was admitted to The Mount Sinai Hospital on January 12, 1939 and discharged improved on January 31, 1939. His present illness started sixteen days before admission, with inability to speak well and right hemihypesthesia.

The patient attended school to the fourth grade in "gymnasium." He left home at the age of seventeen years. Since then he has been a seaman, an instructor in aviation, and during the past ten years, a house superintendent. The latter position was one of some responsibility and trust, and he carried out his duties faithfully and well until the onset of the present illness. He was married 22 years ago when he settled in the United States. There were no children.

He suffered from malaria and yellow fever many years ago. He denied venereal disease. Nineteen years previously he suffered a severe concussion of the brain in an airplane accident following which he was amaurotic for a short period and suffered frontal headaches. However, within the next year he was again quite normal, remaining so until about three years ago. During the past three years he has been subject to frequent, increasingly severe, left supraorbital headaches which were relieved by rest. For the past seven months, since June 1938, he was experienced dyspnea on exertion and constrictive precordial pain radiating to the left arm, both relieved by rest. During the past three weeks, he has experienced left sacro-iliac pain radiating to the left shoulder.

Sixteen days before admission, on December 27, 1938, he was awakened from a sound sleep by "electricity-like" pain in the left sacro-iliac region which radiated up the torso to his head and disappeared in about two minutes. He then experienced the desire to urinate and, after arising from his bed, observed that he was unable to move the entire right side of his body, that he was speechless, and had a right hemihypesthesia. He was put to bed where he remained for about ten days until January 6, 1939. The observations of the patient and his attendants were incomplete with regard to the first three days. The hemiplegia was of very short duration, however, for within one hour the patient was able to move his hand and arm and shortly thereafter was able to write. He knew definitely that he was unable to speak

¹ Presented at the Neurological Conference, January 23, 1939.

at this time and it was necessary for him to communicate his demands to others by writing. However, after three days, though he was able to use his hand well and knew what he wanted to write, he was unable to put the symbols on paper. At this stage his account became more dependable and complete. The paresis and somatic sensory disturbance rapidly regressed and subjectively were completely gone at the time of hospital admission.

Shortly after the onset, the patient experienced continuous loud buzzing in his right ear that gradually diminished in intensity and assumed the character of the ticking of a timepiece. During the early days of his illness as he lay in bed, he repeatedly thought that he was going to die. He frequently thought of his family, mother, father and two siblings who resided in Europe, and felt that if he would die they would also die. When questioned as to the logic of this conclusion, he admitted its fallibility but was unable to elucidate the thought processes which forced the conclusion upon his consciousness. He remembered the visits of his physician, the comforting attention of his wife and friends and various happenings about the sick-room in a straightforward undistorted manner. At no time did he experience any disturbance in special sense perception.

However, beginning on the fourth day of his illness, he noticed an inability to comprehend language symbols. Though he could hear sounds and understand blunt meanings, e.g., a pounding noise meant to him that steam was rising in the radiator pipes (which was true), spoken words were unintelligible to him. He did not observe any difficulty in visual perception until the tenth day of his illness when he attempted to read. He saw the writing well but it had no meaning. Nevertheless, he was able to recognize the meaning and use of objects and pictures and the identity of persons whom he saw at that time. Numbers were meaningless and he could not calculate. After the third day when he became agraphic he could not express himself in language, though crude motions and imitation were possible. He very clearly recounted how he knew what he wanted to say or write, that there was no difficulty in the mental or psychic formulation of words, sentences, or ideas but that their expression in language was impossible. The motor speech component was markedly at fault. There was no apraxia. There was a rapid recession in all these sensory and motor aphasic disturbances during the sixteen days before admission, so that subjectively, when first seen in the hospital, he felt that these functions were approaching normal. None the less he was still subject to thoughts which ran ahead of his speech and writing. As mentioned previously he became conscious of his alexia on the tenth day of his illness. The next day he learned that if he read aloud, the combined sensations of visual and auditory stimuli formed an intelligible image whereas each alone was fairly barren of meaning. At no time in the course of the aphasia was there any dissociation of language.

On about the eighth or ninth day he became conscious of auditory hallucinations in his right ear, limited to the languages of his youth, namely Latvian, Russian and German. The voices were those of his wife, aunt or friends. They spoke intermittently and the context was usually of a consoling nature. They encouraged him, assured him of a rapid recovery, or spoke about unimportant everyday happenings. He experienced these sensations up to the first two days of his hospital stay and then they vanished. He immediately understood their hallucinatory character. From memory he gave a verbatim report of several episodes (translated):

1. While the patient was thinking about his job his wife said: "Don't worry, Ed, you'll live."
2. While thinking about his home a friend said: "You s... of a b... (in a friendly tone), give me back my English cap." This statement referred to an incident which occurred 17 years previously when the patient took a cap from his friend.

3. Referring to a poker game several months ago, a friend said: "You son of a gun, you bluffed me out of two pairs with a pair of deuces."

Since establishing his residence in this country 22 years ago, the patient has learned the English language. During the past ten years he has used it almost exclusively for all his communications. Only infrequently was he called upon to make use of his Latvian. Russian and German had to all intents and purposes become dead languages, for it was on very rare occasions that he heard them and practically never did he converse in them. His intellectual pursuits were moderately varied. He read contemporary and classical literature more than the average person and had a fair-sized library at home. He had always been interested in concert music. In his youth he learned to play the mandolin and balalayka and in recent years he attended musicales as his income permitted. He frequently played the gramophone at home and listened to band and symphonic music over the radio. He thus had a fairly extensive background of music appreciation. He never tolerated ragtime music.

Nine days after the onset of the present illness, January 5, 1939, he listened to radio music for the first time. He was immediately struck by a marked difference in tonal qualities and called this to the attention of his wife. Since that time the observation was repeated several times. Music assumed a new meaning for him. On the one hand he noted an increase in his capacity to appreciate tonal variations and the construction of a musical composition. He observed that he was able to discern more succinctly the function of each instrument in a major musical composition. The qualities of the various string, percussion, and wind instruments were appreciated more keenly. He stated that he became able to understand more clearly the meaning of abstract conceptions expressed musically. Despite these changes with regard to the comprehension of music, he was unable at the same time to understand the meaning of spoken words.

In view of the alleged change in the appreciation of music, it was considered important to determine whether this were a special localized change or whether it represented merely a general increase in affectivity. Though somewhat exaggerated emotional responses could be elicited by detailed probing into the past history, it was the opinion of the patient and the examiner that these were unrelated to the clinical picture, except in so far as such affective changes might occur to anyone confined to bed.

There were no previous memory disturbances, character changes, or disturbances in evaluation or orientation. The patient described a change in the taste of milk so that it resembled that of water but expressed doubt of this change on later examinations.

Examination. The patient was a robust, well developed and well nourished, oriented, cooperative, and intelligent male in no distress. There was no clinical evidence of cardiac disease. Slight tenderness was elicited on deep firm pressure over the left sacro-iliac joint and the left sciatic notch. The Patrick and Lasègue signs were negative.

Neurological examination revealed a right-handed patient. The Romberg sign was negative. The deep tendon patellar and suprapatellar reflexes were sluggish on the left but normal on the right. However, the Achilles jerks were absent bilaterally. The abdominal reflexes were sluggish on the right and normal on the left. A slight diminution in muscle power was elicited in the extremities on the right side, but there were no changes in tone. There was no Babinski sign. Nevertheless tickling was perceived more acutely in the left foot, and in general there was more of a defense reaction to plantar stimulation on this side. The remainder of the somatic sensory examination revealed variable "patchy" areas of slight hypesthesia to pin prick on

the right, and a slight diminution in vibratory sensibility in the fingers of the right hand. The pupils were slightly irregular, of good size, but the right was larger than the left. They reacted well to light and in accommodation. The ocular fundi were normal. The vision was 20/30 in both eyes and the fields for form and color were normal. There was a slight right central facial weakness and auditory sensation was intact.

The speech was slightly telegraphic (language difficulty). He very occasionally used the wrong word in a sentence, or perseverated. At other times, in the course of a conversation, he substituted words in his native tongue for English words. Rarely did he recognize these errors. During a long examination, on occasion he failed to take cognizance of a spoken question. In writing spontaneously, to dictation, or in copying, he rarely erred. His ability to calculate was slightly at fault. There was a very minor diminution in retentive memory. He did not fatigue easily and was interested in the proceedings. There was no apraxia.

Laboratory Data. The blood Wassermann reaction was 4 plus. The cerebro-spinal fluid obtained by lumbar puncture was under normal pressure. It was faintly xanthochromic; the Pandy reaction for globulin was recorded 3 plus; there was a pleocytosis of 88 cells per cu. mm., of which 3 were polymorphonuclear and 20 mononuclear cells. The Lange colloidal gold reaction was 222211000 and the Wassermann 4 plus in 0.1 to 1.0 cc. There were 57 mg. per cent total protein, and 715 mg. per cent chloride as sodium chloride. Roentgenological study revealed a normal skull, a moderately dilated and hypertrophied heart and a tortuous aorta. The electrocardiogram was within normal limits.

Course. At the time of discharge all objective evidence of definite neurological disease had disappeared, with the exception of the absence of ankle jerks and the irregular pupils. The patient was seen three months after discharge at which time his aphasic and other difficulties were gone and he was receiving medicinal therapy for his syphilis.

COMMENT

The episode from which the patient completely recovered has many features in common with other cases of vascular occlusion of known etiology in the brain and in other organs. The sudden onset, the relative diaschisis, the subsequent return of function, and the normal state immediately preceding the stroke are features ordinarily associated with a vascular closure. It is unreliable, however, to attempt too specific an anatomic localization or pathologic change to account for the clinical picture observed in this case of neurosyphilis. Writers (1, 2, 9) on neurosyphilis have cautioned against the attempt to effect too accurate an anatomical or pathological correlation with clinical findings in this disease. Similarly, Head and Fearnside (2) concluded on the basis of an exhaustive clinical and anatomical study that apparently focal and episodic clinical phenomena only too frequently resolve themselves into a widespread fairly evenly distributed process after careful post mortem anatomical study. Campbell (1) studied a series of cases of focal lesions in general paralysis and showed that episodes similar to that observed in this case might at times be correlated with a major vascular narrowing or occlusion of the nature of endarteritis obliterans. But in some of these there was a local

intensification of the pathological changes of dementia paralytica and in a considerable number there was no correlation with local changes.

It is possible that clinical cerebral manifestations of neurosyphilis may be attributed to lesions of the brain which result from functional changes in the cerebral blood flow and not from an organic vascular occlusion. In a series of cases of Lissauer's general paralysis, Merritt and Springlova (3) found lesions in the subcortical white matter involving the short association fibers of the temporo-parieto-frontal junction which could account for the clinical manifestations. However, they were unable to ascertain the pathogenesis of such changes. They suggested vasospasm in the third, fourth and fifth posterior cortical branches of the middle cerebral artery as the probable causative factor. Recent reviews (5) of the functional capabilities and physiological alterations in the cerebral vascular system show that the arterial tree is capable of altering its caliber in response to numerous stimuli. Though it frequently will be impossible to demonstrate cerebral vasospasm in the human, the experimental approach has unequivocally shown that such a reaction can occur. Evidence (4, 6, 7) has been presented that functional and temporary restriction in the cerebral blood flow may lead to irreversible changes in the sensitive cortical cells of the cerebral cortex.

From this discussion, the objections to organic arterial occlusion as the *modus operandi* are brought to the fore. On the other hand it is true that the episode which the patient experienced differed in no essential way from the classical luetic cerebral vascular accident, except in being of wide extent. The absence of unconsciousness in so widespread a disturbance, the rapid regression of signs, and the lack of residua identify this case with familiar transient luetic monoplegias.

The relationship of this case to parenchymatous neurosyphilis is also a close one. Can one be certain that the detailed description of the course of events as related by the patient does not represent parietic trends? The change in music appreciation particularly suggests a grandiose reaction. On several occasions the patient's ability to pun and act facetiously attracted attention. These features in conjunction with the "early parietic," gold curve may actually indicate the presence of paresis. The absence of ankle jerks and the slight pupillary anomalies might be related to tabes or represent a meningeal process. The strongly positive blood and cerebrospinal fluid Wassermann reactions are more in agreement with a diagnosis of general paresis (8), although they do not exclude other forms of luetic disease.

Finally, the possibility that more than one type of lesion of the central nervous system is present cannot be excluded. Campbell's (1) first case is one of a man who suffered a hemiplegia at the age of 33 years, was then well for eight years, at which time parietic features made their appearance. He then progressed through the stages of typical dementia paralytica in

four years. At post mortem examination the brain revealed leutic endarteritis, an old area of softening, and widespread histopathological changes of general paresis.

Before the introduction of the colloidal gold reaction, pentavalent arsenicals and hyperthermia, Head and Fearnside (2) said: "There is not a symptom or sign in dementia paralytica which cannot be present in a case of subacute meningovascular syphilis. Long continued observations of the effects of treatment on the patient and on the Wassermann reaction in the cerebrospinal fluid will separate these conditions of such different prognostic import."

In accord with this discussion, it becomes impossible to be on safe ground with any diagnosis as to the exact form of neurosyphilis. At the present time all that can be said with any degree of certainty is that the patient suffered a disturbance of cerebral function in the region of the quadri-lateral area of Marie. Meningovascular syphilis with involvement of the branches of the left middle cerebral artery is probably present. The patient will be seen from time to time, and the changes in his status noted in an attempt to discover additional data which will permit an extension of the diagnosis.

SUMMARY

This case presented, in a syphilitic patient, global aphasia, hallucinatory episodes, a change in music appreciation, a right hemiplegia and hemihypesthesia with complete rapid functional restitution.

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CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Wednesday, November 22, 1939

Resection of Carcinoma of the Esophagus

[From the Surgical Service of Dr. John Garlock]

History. (Adm. 445668; P.M. 11275.) This was the first admission of a sixty-one year old Irish watchman, who complained of pain at the lower end of the sternum on swallowing. It had first been noticed two or three months before admission and had increased in severity. It was made worse by solid foods so that the patient had restricted himself to liquids for the three weeks before admission. There was no nausea or vomiting, no cough or sputum. He had lost approximately four or five pounds. Constipation had been marked. The past and family histories were non-contributory.

Examination. He was a well developed and well nourished man, in moderate discomfort, but did not appear chronically ill. The trachea was in the midline. Many buckshot-sized lateral and posterior cervical lymph nodes were palpable. The lungs were clear. The heart revealed no abnormalities. On admission the blood pressure was 155 systolic and 100 diastolic. The abdomen was soft. The prostate was moderately enlarged. The neurological examination was negative.

Laboratory Data. Hemoglobin, 98 per cent. Urine, negative. Blood Wassermann reaction, negative. Blood chemistry: urea nitrogen, 13 mg. per cent; sugar, 95 mg. per cent. A barium meal examination showed an irregular filling defect in the lower end of the esophagus about four inches in length, the appearance was suggestive of a neoplasm. Esophagoscopy revealed a sessile tumor mass 32 cm. from the upper incisor teeth and attached to the left lateral wall. Biopsy was reported as squamous cell carcinoma.

Course. The diagnosis of carcinoma of the esophagus was well established by the x-ray, esophagoscopy and biopsy findings. Esophagectomy was decided upon. Therefore, under local anesthesia, a preliminary Janeway gastrostomy was performed. Five days later his temperature, which had been normal, rose to 102°F. It appeared to be the result of a mild wound infection, and it subsided in three days. During this three day period, the patient was extremely lethargic. The blood urea nitrogen at this time was 18 mg. per cent. There was moderate regurgitation of gastric contents through the tube and a slight sloughing of the distal extremities of the gastric tube. Fourteen days later the esophagectomy itself was performed. At this time he lost ten pounds in weight and the hemoglobin dropped to 58 per cent, but he was afebrile. Under avertin cyclopropane anesthesia, resection of the thoracic esophagus was performed. He received a transfusion during the course of the operation and another the same evening. His immediate postoperative condition appeared satisfactory. The next morning his blood pressure was 112 systolic and 50 diastolic; hemoglobin, 63 per cent. His general physical status appeared satisfactory except

that he was unresponsive. During the day he developed loud rhonchi throughout the chest. His blood pressure rose to 180 systolic and 80 diastolic, but increasing evidences of pulmonary edema appeared. In addition there was now present a left facial paresis and depression of the deep reflexes in the left upper and lower extremities. The temperature rose to 100.6°F.; the pulse rate was 140 per minute and the respirations were 48 per minute at the time of his death on the first day postoperatively.

Necropsy Findings. The specimen removed at operation showed a large carcinoma of the *esophagus*. The *lymph nodes* removed at the same time showed no evidence of any metastases. At autopsy the operative bed was clear with no evidence of supuration. There were no evidences of any metastases. There was considerable arteriosclerosis and associated ulceration of the larger vessels. An incidental finding was a left hydronephrosis and a very narrow ureteral ostium.

Comment. *Dr. Klemperer.* The recent advances in the surgical treatment of carcinoma of the esophagus have led to a renewed interest of the pathologist in this condition. Heretofore, one was accustomed to think of esophageal carcinoma as being unassociated with metastases. This apparently is due to the fact that death from this condition resulted too early to allow for metastatic growth. For example, a similar case came to autopsy one year after a successful surgical removal and had extensive recurrence and widespread metastases. It is interesting to note that a carcinoma as large as was present in the case reported here could exist and yet there was complete absence of any metastases. As to the cause of death, although the brain was not examined, a cerebral embolus is most likely on the basis of the marked arteriosclerotic changes that were present.

Dr. Garlock. The enormous size of this tumor is quite surprising in view of the comparatively short history. This may indicate that occasionally very rapid growth of such tumors can occur. Nine resections of the esophagus for malignancy have been performed here with but two operative deaths. The recurrence rate has been highest following operation where the lesion was located between the arch of the aorta and the left branch bronchus. For those tumors situated in the upper two-thirds of the esophagus, a radical esophagectomy must be performed. However, when the lesion is located in the lower third of the esophagus, then an intra-thoracic anastomosis may be performed by pulling a portion of the stomach into the thorax.

Dr. Baehr. Unless cases of esophageal carcinoma come to operation early, there is no point in subjecting them to surgical intervention. Even if resection is successful, the procedure entails a long period of convalescence. Metastases to lymph nodes in the mediastinum occur so early as a rule that all but the earliest cases succumb to metastases by the time they have recovered from the operation. This patient is exceptional for he presented no extension of the carcinoma to the regional lymph nodes in spite of the fact that the primary carcinoma of the esophagus had existed for more than three months.

Reported by *Abner Kurtin, M.D.*

Wednesday, November 29, 1939

Uremia Due to Prostatic Fibroadenoma of Four Years' Duration. Results of Transurethral Prostatectomy

(From the Surgical Service of Dr. A. Hyman)

History. (Adm. 445310; P.M. 11288.) This seventy-two year old man had the first of six admissions to this hospital in March, 1935. At that time his chief complaint was increasing constipation, and the appearance of a painless mass in the lower abdomen which progressively increased in size. There was an associated weight loss of fifteen pounds and increasing asthenia. Physical examination at that time revealed a chronically ill-appearing man. The abdomen was distended and the entire lower abdomen was filled by a large, non-tender, ill-defined mass about the size of a man's head. The prostate was smooth and enlarged to about twice the normal size. The inguinal rings were dilated. The blood pressure was 160 systolic and 80 diastolic. There was marked peripheral sclerosis. The hemoglobin was 50 per cent; the stool guaiac, negative. The urine contained one plus albumin and 15 to 20 white blood cells per high power field, with rare clumps. A barium enema revealed only marked colonic redundancy. The blood urea nitrogen, however, was 85 mg. per cent. It became evident that the large hypogastric mass was a hugely distended urinary bladder. This was, therefore, gradually decompressed and allowed to drain through an indwelling catheter. The blood urea nitrogen slowly fell to 35 mg. per cent. To insure more prolonged and permanent drainage, a stab cystostomy was performed. He was then discharged to be carefully observed until such time as his condition would permit the institution of a procedure for the radical relief of the lower urinary obstruction.

He was re-admitted in June, 1935 for a revision of the original operation, since the suprapubic tube had failed to drain. In the interim a cystoscopy had shown tremendous enlargement of the middle, as well as the lateral lobes of the prostate. His blood urea nitrogen at this time was 38 mg. per cent. In view of this, further procrastination of surgical intervention was deemed in order and he was discharged.

He was again admitted in December, 1935. He was relatively asymptomatic and comfortable. The blood pressure was 150 systolic and 88 diastolic. The prostate was twice the normal size. Renal function tests were performed and revealed an excretion of 10 per cent of phenolsulphonphthalein in three hours; fixation of specific gravity occurred at 1.010, with indigo carmine in only fair concentration one hour after intramuscular injection. The blood urea nitrogen was 35 mg. per cent. Cystoscopy revealed a moderately inflamed bladder with a well-defined median lobe. Although his general status was suitable for transurethral resection, the presence of the poor kidney function and the relative comfort of the patient

weighed against operation. He was, therefore, referred back to the Out-Patient Department.

A transurethral resection was eventually performed in March, 1936, one year after his original admission. Postoperatively, the urea nitrogen which had been 29 rose to 64 mg. per cent. The specific gravity of the urine was fixed at 1.012. With supportive therapy, the blood urea nitrogen approached normal levels. Because of persistent difficulty in voiding, and a demonstrable residual urine of over 30 ounces after removal of the suprapubic tube, a second transurethral resection was performed. At the time of discharge the residual urine ranged from 4 to 6 ounces, the blood urea nitrogen was 27 mg. per cent. In the routine physical examination conducted at this time, a note was made as to the presence of a large right scrotal hernia, and a small ventral hernia.

The sixth and final admission took place in September, 1939. His complaints at that time were exertional dyspnea, as well as marked frequency, nocturia, dribbling and burning on urination.

Examination. The patient was an emaciated white male. The lungs were hyperresonant. The size of the heart could not be determined because of emphysema. The blood pressure was 120 systolic and 86 diastolic. There was a large ventral hernia which contained intestine and possibly urinary bladder. There was an enormous, only partially reducible right scrotal hernia. The prostate was moderately firm and enlarged to twice its normal size.

Laboratory Data. Urine: cloudy, alkaline; specific gravity, 1.012; albumin, 2 plus; and 15 to 20 white blood cells, occasionally clumped. Blood: Urea nitrogen 66 mg. per cent; carbon dioxide combining power, 25 volumes per cent. The phenolsulphonphthalein test showed less than 5 per cent excretion.

Course. On admission his residual urine was found to be over 600 cc. An indwelling catheter was inserted and the fluid intake was increased. The patient became much brighter and more comfortable; there was a drop in blood urea nitrogen. On the eleventh day in the hospital his inguinal hernia became irreducible and tender, and hence operation was undertaken. Under spinal anesthesia, a huge, strangulated, inguinoscrotal hernia was found and reduced. No formal attempt at hernioplasty was made.

Following the operation the patient seemed to do fairly well at first. He ran a low-grade fever, 100 to 101°F. He then developed a marked cough and purulent sputum. On the ninth day a bedside x-ray examination showed a bronchopneumonia of both lower lobes. However, on the eleventh day his temperature became normal and remained so. His condition began to go slowly but progressively down hill. The blood urea nitrogen rose to 119 mg. per cent. Nausea and vomiting developed. His uremia failed to respond to intravenous lactate-saline solution and transfusion. He died four weeks after the hernia operation.

Necropsy Findings. At the bladder neck there was a scar at the site of the transurethral resection. On the left side of the bladder, and connected to the lateral lobe by a pedicle was a large polypoid lesion. On section, this was seen to be composed of prostatic tissue. One could see that on closing the bladder, this tissue was instrumental in producing a severe obstruction. The kidneys showed marked bilateral hydronephrosis, being composed now of only a thin shell of renal tissue. Within this shell was a small, benign, yellow, encapsulated Grawitz tumor. In addition there were evidences of infection in the form of gangrenous pyelitis, and numerous small

abscesses. There were multiple small cysts in the kidneys. The *cecum* and some loops of small intestine were the seat of a necrotizing enteritis.

There was a severe, hemorrhagic pneumonia involving the greater part of the upper lobe of the right *lung*. Extensive fibrosis was found in the anterior wall of the left ventricle of the *heart*; this was secondary to an old closure of the ramus primus of the left coronary artery.

Comment. Dr. Bachr. It is interesting that in spite of a moderate azotemia of four years' duration, this man was kept relatively comfortable during all these years by the use of surgical methods. Today, the operative mortality of prostatic operations has been greatly reduced because of the introduction of transurethral resection.

Dr. Klemperer. There is definite anatomical evidence that the death in this case was a result of uremia, namely, the necrotizing enteritis. The hydronephrosis is obviously a sequel of the longstanding obstruction at the bladder neck.

Dr. A. Hyman. There has been marked and progressive improvement in both technique and results of transurethral prostatic resection. Today, in fact, incontinence is a rare complication, and probably should never occur in a properly executed operation. The chief dangers are still hemorrhage and pyelonephritis. This case was operated on three years ago when the technique was still in the early stages of development. At the present time it would be relatively simple to remove the pedunculated portion. I should like to ask Dr. Klemperer how one can differentiate between a "benign" and "malignant" Grawitz tumor at operation. Obviously such a decision is important since the procedure depends entirely on this fact.

Dr. Klemperer. If the tumor is infiltrating, then of course there is no difficulty. However, an excellent criterion is the size of the lesion. If it be cherry-sized or close to this, then one can be relatively certain it is not a malignant tumor. The incidence of discovery of such benign Grawitz tumors on routine autopsies is surprisingly high.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D., *presiding*

Monday, March 25, 1940

*Case 9.*¹ Metastatic Carcinoma, Multiple, of Cerebellum

[From the Neurological Service of Dr. I. S. Wechsler]

History (Adm. 437122; P.M. 11145). The patient a woman, aged 30 years was admitted to the hospital in March, 1939 complaining of "sciatica" and severe anorexia. In January, 1935 a radical amputation of the right breast had been performed at the Post-Graduate Hospital for a scirrhus carcinoma. She felt well until August, 1938 when she developed pain in the lower back and both thighs following exposure to cold. This "sciatica" continued and was followed by severe pain in the head and neck. She entered the Bellevue Hospital in February, 1939. There, x-ray examinations of the spine, pelvis, chest and skull were found to be negative. A lumbar puncture was also reported to be negative. The patient left Bellevue Hospital without improvement with her anorexia becoming progressively worse so that by the middle of February she was unable to retain any solid food. She then entered this hospital.

Examination. The patient weighed only 80 pounds, she was extremely emaciated. She was oriented in all fields, but uncooperative and at times incoherent. Her behavior was extremely melodramatic. She smiled frequently without apparent cause and she expressed numerous bizarre ideas. There were periods of varying duration during which she appeared to lose contact with her surroundings. The scar of the amputated breast was well healed. Marked hirsutes of the legs and a tendency to male escutcheon were noted. She tended to keep the left eye closed. The reaction of the pupils to light was somewhat limited in excursion. The deep reflexes were all equal and active. There were no objective signs of sciatic nerve involvement.

Laboratory Data. Lumbar tap yielded clear, colorless cerebrospinal fluid under an initial pressure of 90 mm. of water. The total protein was 102 mg. per cent. This was repeated later and the total protein was found to be 62 mg. per cent. The basal metabolic rate was on one occasion minus 10 per cent and on another plus 10 per cent. The Janney test showed a high sugar curve with a 200 mg. per cent maximum at three hours. X-ray examinations of the gastro-intestinal tract were negative. Eye consultation reported the fundi to be normal.

Course. In view of the lack of organic neurological findings and because of the marked emotional conflict which was uncovered by psychiatric consultations it was felt that the patient was suffering from a severe form of anorexia nervosa. The patient was placed on a special diet and given Vitamin B. However, she did not

¹ The first eight cases were presented in previous issues of the Journal (Vol. VII, Nos. 5 and 6; Vol VIII, No. 1).

improve on this regime and about three weeks after admission nystagmus on lateral and upward gaze was noted. At this time, ophthalmological consultation reported the presence of papilledema of one-half diopter in the left eye. It was felt then that the patient might have a lesion in the inter-brain area because of the vegetative disturbances. Encephalography was performed on April 4, but no air entered the ventricular system. A small amount of air was present in the supracallosal sulcus and over the cortex. There was a suggestion of a mass protruding into the cisterna from the posterior aspect. X-ray examination of the skull and lumbosacral spine as well as of the pelvis were negative. X-ray examination of the chest revealed two nodules, one in each lung, measuring about $1\frac{1}{2}$ inches in diameter having the appearance of metastases. The papilledema in the left eye advanced and hemorrhages appeared, while the right eye remained relatively normal. The patient became somewhat euphoric and was able to retain only small amounts of food. She con-

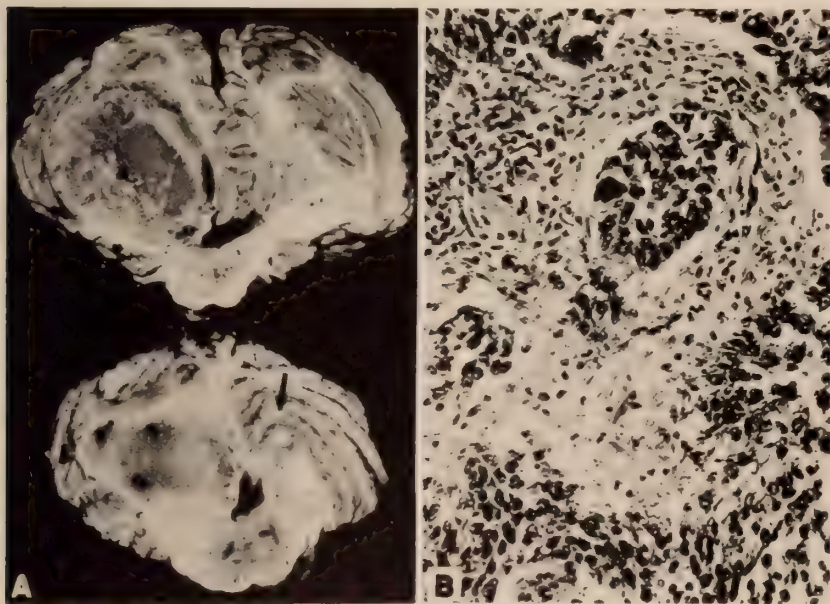


FIG. 14. Case 9. A. Multiple metastatic tumors in the cerebellum. B. Histologic appearance of the metastatic tumor.

tinued to complain of severe headache which occurred paroxysmally and the spells of disorientation decreased in number and frequency. One observer believed there was some weakness of upward gaze and ataxia and adiadochokinesis in upper extremities, more marked on the right. The patient then developed episodes during which she claimed she became blind. On April 18, 1939 the patient developed fever which mounted rapidly and remained elevated. She went rapidly downhill and died April 22, 1939.

Necropsy Findings. Brain. Gross. The external appearance of the brain was normal except for yellowish area over the surface of the right cerebellar hemisphere. This half of the cerebellum was softer than the left.

Upon sectioning the brain, a marked bilateral symmetrical internal hydrocephalus was found affecting the lateral ventricles, the third ventricle and the aqueduct of Sylvius. The fourth ventricle was also somewhat enlarged and was deformed and

displaced to the right. The left cerebellar hemisphere contained a large tumor mass measuring $5 \times 3\frac{1}{2}$ cm. and occupied nearly the entire medullary substance including the dentate nucleus (fig. 14A). The tumor was clearly demarcated from the adjacent brain tissue. The center of the tumor consisted of homogeneous gelatinous material. Surrounding this was pale tumor tissue in which were a few small hemorrhagic areas. Within the cerebral cortex at the dorsal aspect of the lobe there was a small tumor, measuring 1 cm. in diameter. In the right middle cerebellar peduncle there was a similar lesion.

Microscopic. Sections of the tumor tissue in the cerebellum stained with hematoxylin and eosin show the presence of irregular areas of neoplastic cells interspersed with varying amounts of connective tissue (fig. 14B). The neoplastic cells vary in size and shape and in the relative density of chromatin material. Occasionally one sees a clumping together of many cells giving the appearance of multinucleated giant cells. Areas of necrotic tissue are present along with hemorrhages. Throughout the connective tissue stroma there are many thin-walled blood vessels. The tumor is fairly well-demarcated from the surrounding tissue but in the substance immediately adjacent can be seen small groups of neoplastic cells.

Comment. *Dr. Globus:* Little need be added to the facts presented in the account given above. Attention may be drawn to the paucity of objective neurologic findings in the early part of the clinical course in an instance of metastatic brain tumor. This history of primary malignancy elsewhere, as in the breast in this case, should have aroused a strong suspicion of the probable existence of a metastatic focus in the brain. It is highly significant that x-ray examination of the chest disclosed metastatic nodules in the lung, a finding one should look for in any instance of a suspected metastatic lesion in the brain.

Reported by *T. Meltzer, M.D.*

George Blumenthal

April 7, 1858-June 26, 1941

We who have gathered together to do homage to a devoted husband, a loyal friend, and a great humanitarian, are of many faiths but of one fellowship, the fellowship of humanity, and in that fellowship it is fitting that we pause for a moment in meditation and prayer.

We are often told that any man can be replaced. Is this true? Positions can be filled, titles can be transferred, but outstanding men of distinctive personality are never replaced. There was only one George Blumenthal; there will never be another. When that keen mind ceased to function, a great power was lost to the world—a power that had been lavishly exercised, again and again, for the good of mankind.

George Blumenthal had more than an incisive mind; he had an ebullient yet durable energy, an indomitable will, an unassailable integrity, great personal charm, a warm heart. But with all his power, with all his gifts, with all his assurance—so well warranted—in practical affairs, he was one of the most puzzled and in a sense one of the humblest of men. He had sought in vain for the explanation of his own bitter-sweet experiences and of the experiences of others who were dear to him. He was abashed by the inscrutability of Providence, he was dismayed and depressed by the world's disarray, he was disheartened by the suffering of the innocent.

The contemplation of life's vexing problems induced in him, at times, a profound pessimism, but he never permitted himself to sink into futile despair. He might talk like a pessimist, yet his life's work revealed a core of sturdy optimism in his nature, for with persistent hope and determination and with unflagging energy, he sought to improve the lot of the unfortunate.

Essentially a man of action, he was impatient of needless delays. When there was a task to do, he wanted it done promptly. There were moments when he was brusque, but beneath his sharp and vibrant executive manner there was a warm and everlasting spring of tenderness. His friends had ample reason to know that no one could be more thoughtful, more considerate of others.

George Blumenthal's publicly known benefactions were impressive in their scope, yet they reflected only a small part of his great and far-flung generosity. To understand this side of his character more fully, one would have to know how often, behind the scenes, he extended a helping hand to persons in distress. And such help was given kindly, with courtesy, often anonymously.

It was to America and to American institutions that he owed his greatest opportunities, and this obligation he sought to repay by every means at his command.

When George Blumenthal joined a working group, his qualities of leadership soon came to the surface, and this happened without aggressiveness on his part. Men turned to him instinctively when they saw how quickly he grasped a situation, how just was his attitude, how sound his judgment, how inexhaustible his energy, how successful he was in getting things done.

He gave and inspired the utmost loyalty. Wherever he happened to be, friends soon surrounded him. His friends were confined to no race and to no class.

He was eager to spread the blessings of health and the delights of beauty. He never relinquished the hope that through the advance of science all men might be enabled to share in the solid satisfactions of health, and he believed that all men should do so.

Always sensitive to beauty, he was particularly responsive to beauty that was man-made. He derived endless pleasure from beautiful objects of art that reflected the creative ability and the superlative skill of authentic genius. There was a kinship between his wish to popularize art, to give to the humblest citizen the opportunity to share in its enjoyment, and his struggle to bring about a wider distribution of health.

To us who loved George Blumenthal for what he was, for what he did, for what he suffered, for his efforts to alleviate the sufferings of others; to those who rejoiced in the prolongation of his active and fruitful life; to her with whom he spent his last years in close communion and in the shared realization of spiritual values derived from his long and wide experience, this is a poignant moment.

To us George Blumenthal will remain a tender and a treasured memory, a life-long inspiration. There will never be another George Blumenthal. May he rest in peace.

S. S. GOLDWATER, M.D.

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Visceral Complications in Tuberculosis of Bones and Joints. H. R. LANDMANN.
Am. J. Surg. 44: 569, June 1939.

The predominantly found visceral complication of skeletal tuberculosis was the secondary tuberculous involvement of the genito-urinary tract. Ten out of 159 cases with definitely proved skeletal tuberculosis showed visceral complications. Five of these ten cases suffered from genito-urinary tuberculous involvement. The cases were almost evenly divided between the sexes and the age group of 25 to 40 years was mostly involved.

As several authors reported the frequency of genito-urinary complications in tuberculosis of bones and joints repeated urine examinations for acid fast bacilli are suggested to discover early complications before the onset of clinical manifestations.

The Intestinal Phase in Urologic Disease—The Role of the Colon in Uroinfections.
R. TURELL. Am. J. Digest. Dis. & Nutrition, 6: 312, July 1939.

A careful review of the literature as well as a personal study of cases was presented to show that stasis of fecal current and anorectocolonic inflammatory and suppurative disease may initiate and perpetuate uroinfections in certain cases. In the consideration of urinary tract infections, it is surprising to note that in the past little significance has been attached to the inflammatory and suppurative anorectocolonic infections lesions. It was suggested that inflammatory and suppurative proctologic lesions should be searched for and properly evaluated in all cases of uroinfection, especially in the acute and recurring types of pyelonephritis caused by the organisms of the colon bacillus group.

The treatment of the cases under discussion consisted of colonic irrigation, castor oil catharsis, agar-agar, acidophilus milk, anti-constipation diet, and the eradication of anorectocolonic inflammatory and suppurative disease. The disappearance of the pathologic elements of the urine was gradual, and at times very slow, requiring several months. As these patients responded to the treatment directed to the colonic lesion alone, they were not considered primary urologic problems.

Insensible Perspiration in Children. G. J. GINANDES AND A. TOPPER. Am. J. Dis. Child. 58: 71, July 1939.

Studies of the effect of certain sympatheticomimetic and vagomimetic drugs on the insensible perspiration and heat production of children are reported.

The drugs used for these studies were atropine sulfate, pilocarpine hydrochloride and epinephrine hydrochloride. Within the range of the dosage employed, atropine,

pilocarpine and epinephrine induced a disturbance in the correlation between the insensible perspiration and the basal metabolism. Atropine and epinephrine uniformly decreased the insensible perspiration. Pilocarpine increased the insensible perspiration. The basal metabolism was uninfluenced by atropine and pilocarpine and slightly increased by epinephrine.

The facts obtained confirm the previously elaborated conception as to the mechanism of the insensible perspiration and emphasize the important effect of alterations in the vegetative nervous system on the insensible perspiration.

Peri-anal Tuberculosis. E. GRANET AND J. GERENDASY. Quart. Bull., Sea View Hosp. 4: 445, July 1939.

Peri-anal infections occur in 5-10 per cent of patients with pulmonary tuberculosis as contrasted to 0.5 per cent in the non-tuberculous population. Seventy-five per cent of fifty patients with pulmonary tuberculosis who were operated on for peri-anal infections, showed tuberculous granulation tissue histopathologically. In this series, multiple lesions, i.e., abscesses and fistulae, were the most common. Lesions were frequently extensive and spread occurred along the course of the superficial peri-anal lymphatics. Conservative surgery is futile in the treatment of peri-anal tuberculosis as shown by persistence of pathology in 40 per cent of their patients previously operated on elsewhere. Effective treatment demands radical excision of all existing pathology. Foci of tuberculous granulation tissue must be carefully sought for in the wound and completely eradicated when found. Operation in stages is indicated when lesions are extensive. Radical measures as described, when instituted early, should result in a high percentage of cures (90 per cent).

The Effect of Castration on Tubal Contractions of the Rabbit, as Determined by the Rubin Test. S. WIMPFHEIMER AND M. FERESTEN. Endocrinology, 25: 91, July 1939.

The character of tubal contractions of 18 living castrated rabbits was compared with that of an equal number of control animals, by uterotubal carbon dioxide gas insufflation. After castration, the contractions were less frequent and weaker.

The administration of estrogenic hormones to 14 castrated rabbits resulted in an increase in the rate and height of tubal contractions. The addition of progesterone to 6 of these animals, sensitized with estrogenic substances, resulted in a diminution of the contraction rate in 3 instances and no variation in the remaining 3.

After castration, the tubal mucosa of rabbits became atrophic and the muscular layer thin. Following injections of estrogenic hormones and progesterone, the tubal mucosa of castrates became hypertrophied and the muscular layer thicker.

Basal Metabolism of Tuberculous Children. II. *Afebrile Primary Pulmonary Tuberculosis.* A. TOPPER AND J. SHORE. Am. J. Dis. Child. 58: 119, July 1939.

For the past three years extensive studies have been made of the basal metabolism in children with tuberculosis.

Children with active afebrile primary pulmonary tuberculosis have an increased basal metabolic rate as long as there are signs of activity of the disease process. When the process becomes inactive as evidenced by absence of physical signs, negative roentgenogram, and a normal sedimentation rate, the basal metabolism returns to a normal rate.

It is believed that the basal metabolic rate is a diagnostic criterion of activity or inactivity of a primary lesion.

This does not however apply to the adult type of tuberculosis in which the rate remains normal even in the presence of extensive pulmonary pathology.

Absorption Lines of the Cornea. J. LAVAL. Arch. Opth. 22: 257, August 1939.

The above mentioned condition occurs in old corneal scars following inflammation

of the cornea in childhood. The scar which is produced in childhood is more easily vascularized and in the region of the blood vessels some of the inflammatory tissue is absorbed, leaving clear lines. In these clear lines in the cornea the obliterated vessels can still be seen. This absorption does not occur in adults because the wandering cells and the fixed cells of the cornea are much fewer in number in adult corneae. A case is reported and the literature is reviewed.

Granulocytopenia Caused by Sulfapyridine in Children. N. ROSENTHAL AND P. VOGEL. J. A. M. A. 113: 584, August 1939.

The prolonged and intermittent use of sulfapyridine in children may cause damage to the hemopoietic system and consequent development of granulocytopenia.

The toxic action of sulfapyridine resembles, to a great extent, the effects of neorsphenamine. With both, the bone marrow changes are rather definite and vary from a maturation arrest to a distinct, almost complete suppression or hypoplasia of all the elements. In one infant who recovered, there was a granulocytopenia with a marked increase in monocytes in the peripheral blood. The sternal marrow revealed a decrease in the total nucleated count with an increase in myelocytes. In the two fatal cases, one showed a severe depression of the myeloid elements with a relative increase in lymphocytes and normoblasts. In the other, the effect was still more marked with a hypoplasia of all elements and an increase in the number of reticulo-endothelial cells.

Further Notes Concerning Traumatic Subdural Hematoma. S. W. GROSS. Radiology, 33: 213, August 1939.

Twelve cases of traumatic subdural hematoma are reported, 8 males and 4 females. In every instance, but one there was a history of an injury to the head. In most cases there was a latent period of several days before the onset of symptoms. An average of about $3\frac{1}{2}$ weeks elapsed from the time of the accident to the time of operation. Four patients were in deep coma when first seen, six were in stupor, and two had no alteration in the state of consciousness. Headache was a prominent symptom in every case but one. There was a bradycardia in 8 of the cases. A dilated pupil was found on the side of the lesion in only 3 cases, in 2 the large pupil was on the normal side. In 50 per cent of the patients hemiparesis and increase in reflexes was found contralateral to the lesion; in 25 per cent the hemiparesis was homolateral, in the remaining 25 per cent there was no weakness or reflex change. Severe papilledema was found in only 2 cases.

The cerebrospinal fluid was clear and colorless in 7 cases, xanthochromic in 4, and bloody in one. The cerebrospinal fluid pressure was measured in 8 cases. In 4 it was above 180 mm. of water. X-ray of the skull showed a fracture in only 2 cases.

Operation was carried out in every case. Eight patients made satisfactory recoveries. Four patients who were in deep coma at the time of operation died. The author recommends bilateral transtemporal trephine exploration under local anesthesia whenever a traumatic subdural hematoma cannot be eliminated in the differential diagnosis.

The Intestinal Phase in Urologic Disease. R. TURELL AND A. W. M. MARINO. J. Urol. 42: 197, August 1939.

Evidence was presented to indicate the existence of a close relationship between the intestinal and urinary systems. It was shown that pathologic activity in the digestive tract, especially in the colon, rectum, and anus, under certain circumstances, can produce disease in the urogenital tract. It was pointed out that disease in one system may mimic a pathologic process of the other system. It was also shown that it is impossible at times to satisfactorily explain a disease process by a

study of one organ or one system of organs. Therefore, the investigation of "system pathology" and "system diagnosis" was advocated.

Partial Thoracoplasty (with Extrafascial Apicolysis) and Contralateral Oleothorax.
A. H. AUFSES. J. Thoracic Surg. 8: 615, August 1939.

Two cases are presented in which partial thoracoplasty with the "Semb" technique was performed in the presence of a contralateral oleothorax. As far as could be determined this combination of bilateral collapse methods had not been previously reported in the literature. The advantages to be derived from a contralateral oleothorax (in preference to pneumothorax) during the performance of thoracoplasty in bilateral disease are presented.

In one case the oleothorax was used as a procedure of choice, in the other it was necessary because of an obliterative pleuritis. In spite of a very low vital capacity both patients had uneventful postoperative courses following each stage of a two stage thoracoplasty. The final result in one was excellent with no visible cavity and negative sputum; the other refused a necessary third operation and has a small patent residual cavity.

Primary Carcinoma of the Common Bile Duct; Resection; End-to-end Anastomosis.
J. H. GARLOCK. Ann. Surg. 110: 474, September 1939.

The author reports a case of primary carcinoma of the common bile duct treated by resection and end-to-end anastomosis of the common duct. Convalescence was uneventful and the patient was discharged from the hospital on the thirty-eighth day. The author calls attention to the fact that too great reliance should not be placed upon laboratory tests in differentiating obstructive jaundice from jaundice of hepatogenous origin. He stresses the rarity of radical surgery when a patient first comes for relief of the jaundice

A New Colostomy Spur-crushing Clamp. J. H. GARLOCK. Surgery, 6: 428, September 1939.

The author reports a new spur-crushing clamp for use in surgery of the large bowel after the performance of the Mikulicz operation. The clamp is characterized by its simplicity and efficacy.

Massive Dose Chemotherapy of Early Syphilis by the Intravenous Drip Method. H. T. HYMAN, L. CHARGIN, J. L. RICE AND W. LEIFER. J. A. M. A. 113: 1208, September 1939.

Eighty-six cases of primary and secondary syphilis were treated by the intravenous drip method, an average dose of 4.0 Gm. of neoarsphenamine being given in a period of less than five days. Of the seventy-eight patients in this series observed over a long enough period of time, seventy (90 per cent) are apparently "cured," four more show a definite serologic trend toward negativity, and four are failures. These results compare favorably with those obtained by the routine continuous method of therapy.

There were minor and major toxicologic effects, the most important being one fatality due to hemorrhagic encephalitis, and the occurrence of peripheral neuritis in thirty-one of the patients. This latter complication was in most instances mild, always sensory, and cleared up spontaneously in from three to six months. There also occurred four cases of mild jaundice, all of whom made prompt uneventful recoveries.

These investigations are being continued, with modifications which are reducing the incidence of toxic effects.

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CONTENTS

	PAGE
ALEX MOSCHCOWITZ. MY FRIEND. <i>Howard Lilienthal, M.D.</i>	121
AN APPRECIATION OF DR. ALEXIS VICTOR MOSCHCOWITZ. <i>M. G. Seelig, M.D.</i>	123
A MODIFICATION OF THE MOSCHCOWITZ OPERATION FOR FEMORAL HERNIA. <i>Harold Neuhoﬀ, M.D.</i>	125
LATE SEQUELAE OF STRANGULATED HERNIA WITH A REPORT OF TWO ILLUSTRATIVE CASES. <i>Percy Klingenstein, M.D., and Ralph Colp, M.D.</i>	129
EXTRADURAL VARIX SIMULATING HERNIATED NUCLEUS PULPOSUS. <i>Ira Cohen, M.D.</i>	136
INTERSTITIAL HERNIA. <i>Ernest E. Arnheim, M.D.</i>	139
ASYMPTOMATIC TRAUMATIC DIAPHRAGMATIC HERNIA MISTAKEN FOR PULMONARY TUBERCULOSIS. <i>Arthur H. Aufses, M.D.</i>	143
COMPLETE DIVISION OF THE SPERMATIC CORD IN CONJUNCTION WITH INGUINAL HERNIOPLASTY. <i>William H. Mencher, M.D.</i>	149
PUNCTURE OF THE EXTERNAL ILIAC ARTERY AND VEIN DURING INGUINAL HERNIOPLASTY. <i>Gabriel P. Seley, M.D.</i>	152
DIRECT HERNIA IN THE FEMALE. <i>Leon N. Greene, M.D., and Harold Neuhoﬀ, M.D.</i>	155
HERNIA IN THE LINEA SEMILUNARIS. <i>Irving A. Sarot, M.D.</i>	164
AN UNUSUAL TYPE OF DIRECT INGUINAL HERNIA. <i>Seebert J. Goldowsky, M.D.</i>	167
HERNIATION OF THE URINARY BLADDER. <i>Jack H. Levy, M.D.</i>	170
INCARCERATED FEMORAL HERNIA CONTAINING AN ADHERENT APPENDIX. Report of Two Cases in Men. <i>Gabriel P. Seley, M.D.</i>	175
REDUCTION EN MASSE OF A STRANGULATED HERNIA. OPERATIVE CURE. <i>Jerome S. Coles, M.D.</i>	178
STRANGULATED RICHTER'S HERNIA. OPERATIVE TREATMENT BY LAPAROTOMY. <i>Harold Neuhoﬀ, M.D.</i>	181
THE WILLIAM HENRY WELCH LECTURE. I. THE CONDITIONS DETERMINING CANCER. <i>Peyton Rous, M.D.</i>	184
THE WILLIAM HENRY WELCH LECTURE. II. THE KNOWN CAUSES OF CANCER. <i>Peyton Rous, M.D.</i>	186
VITAMIN D THERAPY. <i>Benjamin Kramer, M.D.</i>	188
THE ORGANIZATION OF THE BLOOD BANK AT THE MOUNT SINAI HOSPITAL. Observations and Results from June 1938 to June 1940. <i>N. Rosenthal, M.D., L. R. Wasserman, M.D., H. Abel, M.D., F. Bassen, M.D., and P. Vogel, M.D.</i>	210
CLINICAL PATHOLOGICAL CONFERENCE.....	232
CLINICAL NEUROPATHOLOGICAL CONFERENCE.....	238
ABSTRACTS.....	248

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Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of The Mount Sinai Hospital, Mt. Royal and Guilford Avenues, Baltimore, Maryland, or 1 East 100th Street, New York City.

DEDICATED
TO THE MEMORY OF
THE
MASTER IN THE FIELD OF HERNIA
AFFECTIONATELY KNOWN TO A HOST AS
A. V.



Alexis Victor Moschowitz
April 25, 1865-December 21, 1933

ALEX MOSCHCOWITZ

MY FRIEND

More than seven years have gone since we lost the friendly and professional companionship of Alexis Moschcowitz; but he is so often in the thoughts of those with whom he worked and played that it is hard to realize he will not return. He has left so much of himself in scientific spirit and original contribution to his beloved Surgery that his place has become permanent and individual. Nor is it necessary to present here a catalogue of his works; they form an imposing group in every library of Medicine where those desiring to gain valuable information will find it. His work in hernia will, doubtless, be noted by other writers in this commemorative volume.

My first meeting with Dr. Moschcowitz was in the old East Thirty-fourth Street New York Polyclinic where I had a little out-patient class for minor operations. The classes were most informal and the students, all graduates in medicine, from many regions of our country were encouraged to question or discuss what was being done for the patients, whether operative or not. Advice or suggestion from the benches was welcome.

Alex and I had a good time and the more I saw of him the more I appreciated his humor and his originality. One day a red-faced woman from Britain or one of its neighboring islands brought an injured finger for treatment. She had, obviously, taken an overdose of some agreeable stimulant either before or after the accident.

As we were preparing to operate under local anesthesia, a white rabbit from the near-by animal house appeared in the room. There was a curious expression of alarm, almost panic, in the face of our patient. "What's that?" inquired Dr. Moschcowitz, pointing toward the animal. "Sure," said she, "It's a rabbit— isn't it?", after careful scrutiny of the quadruped. Dr. Alex, moving slowly toward the door of entrance gazed earnestly and returning, with a smile of reassurance, informed our patient that it was, indeed, a rabbit. There was a sigh of relief when the lady realized that she was not experiencing an hallucination. And the operation proceeded.

Arpad Gerster, one of the first in America to practice and preach true aseptic surgery and who was the author of valuable and beautifully illustrated books on the subject, learned to know Alexis Moschcowitz, then an Intern in what in those days was The German Hospital. The conscientious and untiring zeal of the young surgeon was greatly admired by Gerster who often spoke to me about him and at last welcomed his

appointment on the surgical staff of The Mount Sinai Hospital. There, Moschcowitz rose by stages to the Attending Staff and reached the important grade of Consulting Surgeon.

It was at Mount Sinai that I came in close contact with him. He was the friend of everyone. The nurses, who were, perhaps, able to observe Dr. Moschcowitz's sympathetic care of the patients and the cordiality of his relations to all, noted, too, the results of his surgical care; quite naturally, therefore, he developed a flattering practice among the graduates of the Training School—as it was called in those days. A pair of attractive twin graduates of the School were so nearly alike in appearance that it was not until a Moschcowitz appendicectomy scar appeared that one could distinguish them—and then only with unusual difficulty.

His manner of carrying on discussions in professional bodies was always a joy. I well remember how bluntly yet with what fascinating tact he disagreed or, rather, corrected one of the grave and reverend seniors of the American Surgical Association. It seems to me that this was at his first meeting as a Fellow of that distinguished body. Dr. X. had described a manner of operating in the upper abdomen and had illustrated his talk with an explanatory drawing on the black-board. When the paper was thrown open for discussion Alex rose to be recognized and going to the black-board with an apologetic smile on his face, "That is the anatomy as Dr. X. has shown you," he said; "but I think it is this way." And, with a few strokes of the chalk he diagrammed a relation of the parts which was obviously the correct one. This was accomplished in such a spirit of humor and good nature that from that moment Dr. X. became his friend and champion.

In addition to scientific knowledge and technical skill the surgeon must recognize the importance of the psychic approach in order to allay the natural alarm of the patient contemplating an operation. His confidence in the man who is to undertake the task will often make all the difference between success and failure.

More than once Dr. Moschcowitz has been my fortunate choice when dealing with surgical disease in those whom I love.

Howard Lilienthal

AN APPRECIATION OF DR. ALEXIS VICTOR MOSHCOWITZ

I am asked to contribute a few introductory remarks to this issue of the *Journal* which memorializes a part of the life work of Alexis V. Moschcowitz. I undertake to do this with the inevitable timorousness accompanying all efforts that end up in cold type; and yet with a certain pardonable assurance that no one could perform the task with a larger measure of enthusiastic and sympathetic understanding.

My acquaintance with A. V. Moschcowitz began in the summer of 1900 when he was adjunct surgeon and I was a recently appointed externe to The Mount Sinai Hospital. In me, as in everyone else whose orbit touched his, there sparked joy and warmth at the first contact. It was typical of the man to inspire such a reaction. And after having been embraced in the sphere of his personality, one inevitably experienced the development of an indefinable variety of affectionate admiration for the man. Any picture that leaves out this attribute fails to show the real measure of Moschcowitz, so large a part of whose nature was the reciprocal love of him for man, and man for him.

Likewise a picture of him would be flat and colorless if it did not portray the joy of life that he found in his work. Thoroughness of understanding and painstaking accuracy of execution were so much of the nature of passions with him, that they not only colored his thought processes and his surgical performances but also overflowed into the broad channels of inspiration to those who worked with him. Whenever I read about the influence of a Cooper, Abernathy, Syme, Liston or Lister (to mention only a few that come into mind at random) on younger co-workers, I am reminded of Moschcowitz in his relationship to his younger colleagues. If there be a sounder basis on which to rest the hope for immortality than that of having inspired and indoctrinated youth, I know not what it is.

Just one other word in the character picture of the man. The late Dr. John Chalmers Da Costa once told me that although he preached the gospel of the uselessness of surgical worry, he, nevertheless, was always careful to select a "worrying surgeon" to care for the Da Costa family's surgical ailments. Moschcowitz was a "worrying surgeon." Not he, the utilitarian worrier, who translates phantom fears into matters of personal consequence; he was the type of constructive thinker who cannot rid himself of the load of threatening disaster until he has struggled to grasp the underlying cause or causes and to establish present and future preventive procedures. Thrice blessed the patient whose welfare rests in the mind, heart and hands of such a surgeon.

No field of surgery was alien to Alexis Moschcowitz: a fractured femur, a ureteral calculus, a spinal cord neoplasm, any type of thoracic or abdominal lesion,—'twas all in the day's work during a large part of his active career. But the field which, more than any other, he elaborated and indelibly impressed, was the one that concerned the cause and cure of hernia. Inguinal, femoral, umbilical, incisional, ventral, obturator, incarcerated, strangulated, sliding and all other varieties of hernia came, at one time or another, under the nib of his pen; and so likewise, at one time or another, almost every variety of hernia came under the strokes of his scalpel, for he was an incomparably fine herniotomist. It would be difficult to select a better example than that furnished by Moschcowitz in his hernia work, of the rare and happy combination of the academic and the practical surgeon; a dualism always devoutly to be hoped for.

That the Journal of The Mount Sinai Hospital should see fit to memorialize the fine spirit and attainments of Alexis Moschcowitz is striking evidence of the dogged persistence of the nobler motivations in life.

M. G. SEELIG, M.D.

A MODIFICATION OF THE MOSCHCOWITZ OPERATION FOR FEMORAL HERNIA

HAROLD NEUHOF, M.D.

The operation devised by A. V. Moschcowitz through an inguinal approach was intended as a precise and definitive solution of the problem of femoral hernia. It made feasible not only a truly high ligation of the neck of the sac but also a satisfactory surgical management of the contents of the sac in cases of irreducible or strangulated femoral hernia. For these



FIG. 1. The landmarks in the male are indicated with Poupart's ligament as a double dotted line. The inguinal incision is lower than usual. In the insert are indicated: (A) the stump of an ablated indirect sac, (B) the bulge of a direct hernia, and (C) the stump of an ablated femoral sac as it existed.

reasons it represented an advance over the customary Bassini hernioplasty performed in the upper portion of Scarpa's triangle. The latter type of operation suffices for the cure of femoral hernia in the great majority of instances, according to the opinion of some observers who believe the Moschcowitz operation therefore is unnecessary. However, the chief objection to the ingenious procedure originated by Moschcowitz is that the inguinal canal

is laid open in order to expose and ablate the femoral sac, and as a result the development of an inguinal hernia is invited. Indeed, instances of inguinal hernia following the Moschcowitz operation for femoral hernia have been noted. As a result, the operation has not been as widely practiced as otherwise might have been the case.

In order to restore the Moschcowitz operation to the place which it warrants, an effort has been made to modify that aspect of the procedure which invites the possibility of formation of an inguinal hernia. It will be

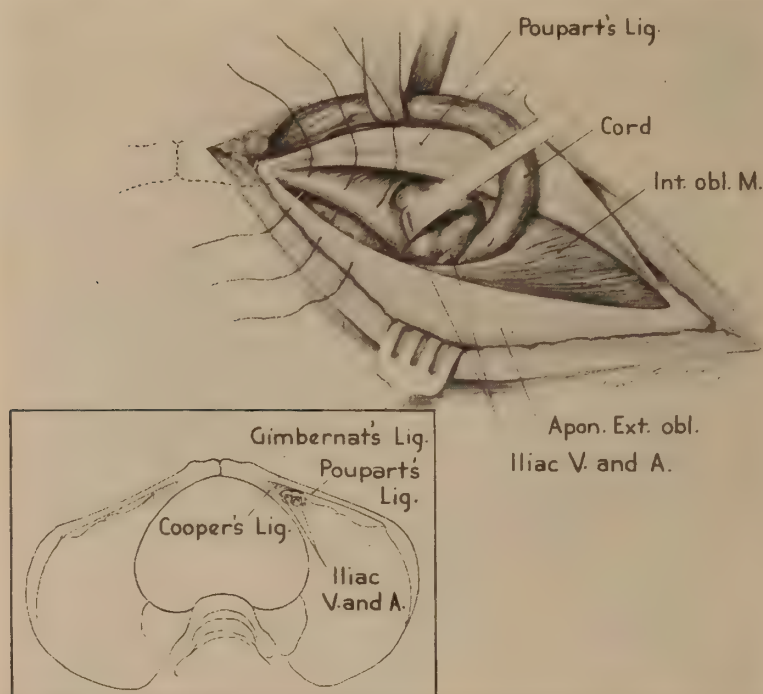


FIG. 2. Three sutures are passed between the aponeurosis of the external oblique and Cooper's ligament. Some of the fibers of Gimbernats' ligament often can be included with advantage, but Poupart's ligament is not included.

recalled that the operation, having laid open the inguinal space, is terminated by approximating the aponeurosis of the external oblique to the reflected surface of Poupart's ligament. A shelf is thus constructed which closes the inguinal canal, but the dead space necessarily manufactured in the exposure of the femoral sac and adjacent structures is not obliterated and hence is the potential site for an inguinal hernia. The dead space is effectively obliterated, at least in large part, by the following modification of the placement of sutures for the closure of the inguinal canal: the thin but definite fibrous membrane medial to the iliac vein and immediately adjacent to the deepest portion of the reflected surface of Poupart's liga-

ment is traversed bluntly, the instrument following the continuation of Poupart's ligament into the pelvis in the form of Cooper's ligament. The latter is exposed to its attachment to the pubis, for it is Cooper's and not Poupart's ligament which is to be utilized primarily for the attachment of the external oblique aponeurosis. With gentle lateral retraction of the

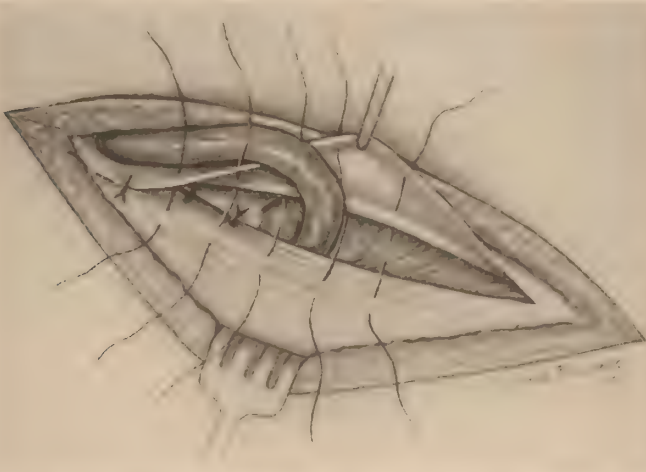


FIG. 3. The deep sutures have been tied. The reflected surface of Poupart's ligament is approximated to the adjacent aponeurosis of the external oblique by a second layer of sutures. Complete closure can be made in the operation for femoral hernia in a female.

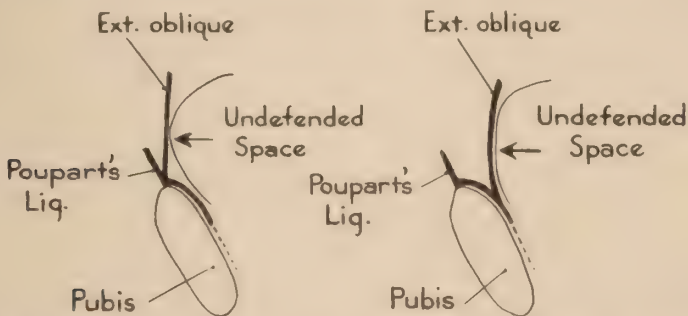


FIG. 4. Diagram to illustrate the difference in effect between the conventional type of operation and that described in the text. Vertical section. On the left the external oblique is attached to the deepest portion of Poupart's ligament, Cooper's ligament not being utilized. The undefended space is not well supported. On the right the external oblique is brought to Cooper's ligament, Poupart's not being utilized (in the first layer). The undefended space is well buttressed.

external iliac vein, there is exposed an area of Cooper's ligament sufficient for the placement of two or three sutures which hug the periosteum. When these sutures are tied, the external oblique is drawn downwards and inwards in the form of a sling, thus buttressing or obliterating the dead space. Incidentally, an assurance against recurrence of the femoral hernia is given

by the support obtained for the stump of the femoral sac by this fascial or aponeurotic sling. The next step is the attachment of Poupart's ligament to the external surface of the sling, thereby reinforcing the support of the inguinal canal. In view of the necessity for the absence of tension on the line of approximation of the external oblique to Cooper's ligament, an adequately mobile flap of external oblique aponeurosis is required. This should be provided for at the outset of the operation by opening the inguinal canal at a lower level (nearer the inguinal fold) than is usually chosen. Another feature to which reference may be made is the use of the Reverdin needle for the convenient passage of the deep sutures through Cooper's ligament.

The foregoing modification is really not a modification of the Moschcowitz operation for femoral hernia, but a modification of the standard method of closure of the inguinal canal. As such, however, because of the greater assurance that is offered against the evolution of an inguinal hernia, it should provide justification for a wider application of an otherwise highly satisfactory surgical operation for femoral hernia.

LATE SEQUELAE OF STRANGULATED HERNIA WITH A REPORT OF TWO ILLUSTRATIVE CASES

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[From the Surgical Service of Dr. Ralph Colp]

The complications arising in strangulated hernia are usually manifested in the immediate postoperative period. The mortality associated with this accident, aside from cardiac and respiratory complications incident to the more advanced age groups in which strangulation most often occurs, is due to progressive damage to the bowel incident to a compromised blood supply. The emergency can be met by prompt operation with release of the constricted gut before irremediable changes have taken place. The extent of the vascular damage to the hollow contents of the sac is usually appreciated by the surgeon at operation. The decision to replace the bowel after relieving the constriction or to extirpate it with or without the reestablishment of intestinal continuity is not always a simple one. Attention to certain criteria will aid in arriving at a proper decision but even the most experienced will fail to appreciate the extent of bowel damage in some instances. Postoperative intestinal paresis and peritonitis with a fatal termination is frequently an indication that reduced hernial contents were non-viable. Fortunately in rare instances the processes of repair and destruction in damaged bowel are equally balanced so that chronic progressive rather than acute necrotic inflammatory changes take place, manifesting themselves late after operation with a resultant train of symptoms which we have learned to recognize and combat. Two such cases have recently been encountered and furnish the basis of this report.

CASE REPORTS

Case 1. History (Adm. 431574). S. B., a male, 50 years of age, referred by Dr. Saul Jarcho, was admitted as a private patient to The Mount Sinai Hospital on October 30, 1938. Fifteen hours before admission, the patient had developed severe abdominal pain, at first localized to the epigastrium, and then radiating to the right lower quadrant. Vomiting soon occurred. There were no bowel movements for the twenty-four hours prior to admission. A hernia which was present for many years following an appendectomy twenty-eight years before began to bulge.

Examination. At the time of admission the patient was an acutely ill man rolling about in the dorsal recumbent position, vomiting at intervals. There was slight abdominal distention of the upper abdomen, but no visible peristalsis. In the right lower quadrant, immediately distal to an oblique appendicectomy scar, was a mass about 18 cm. long and about 6 cm. wide. The mass was firm and somewhat tender. The rectal examination was negative. The pulse was 100 per minute; temperature, 100°F., and respirations, 20 per minute. The urine was acid; specific gravity, 1.032,

with a slight trace of albumin. The blood urea nitrogen was 19 mg. per cent, and the chloride 530 mg. per cent.

Operation. This was immediately performed under spinal anesthesia. Just below a right McBurney incision was a firm irregular grapefruit-sized irreducible mass. The scar was excised and the hernial sac exposed. The contents consisted of omentum which was injected and presented several areas of purplish ecchymosis. The strangulated bowel which was about a foot in length was injected, indurated, and was deeply cyanotic in several large areas. However, after treatment with hot saline for about five minutes, the color of the loop became noticeably pinker and the purplish areas disappeared. The pulsation of the mesenteric vessels in the region of the affected bowel was palpable. Part of the omentum was resected and the loop of



FIG. 1. X-ray showing barium introduced through Miller-Abbott tube. Arrows point to strictured areas in ileum.

bowel was returned within the peritoneal cavity. The hernial sac was removed and the peritoneum was sutured as a separate layer with continuous chromic catgut; the overlying transversalis fascia with some muscle was sutured with interrupted chromic sutures. The aponeurosis of the external oblique was then overlapped and the skin closed with pincettes.

Postoperative course. Following operation the patient was given continuous intravenous saline and an indwelling Levin tube was introduced. The Levin tube was removed on the fourth day and the following day a spontaneous bowel movement occurred.

The wound healed by primary union and the patient was discharged on the fifteenth postoperative day, November 15, 1938.

The patient was readmitted four days later, because fifteen hours before he had begun to experience mild cramp-like pain in the epigastrium and periumbilical region. This pain came in short sharp attacks and was associated with weakness and profuse sweating. There had been no vomiting and no bowel movement in the previous twenty-four hours.

Examination revealed a rather dehydrated patient who was undoubtedly suffering from an incomplete intestinal obstruction. There was very little epigastric tenderness, no distention and no visible peristalsis. The previous wound was healed. He was placed upon intravenous saline; a Miller-Abbott tube was introduced successfully and within twenty-four hours there was a spontaneous bowel movement. A thin barium solution was then introduced through the Miller-Abbott tube and roentgenograms were made (fig. 1). The roentgenologist reported that a short distance from the tip of the tube there was a narrowed segment of ileum followed by a slightly distended segment about four inches in length. The barium did not progress beyond the latter segment for about thirty minutes, then it slowly passed and was eliminated through the stool the next morning. The appearance suggested a narrowed segment of the ileum near the tip of the tube and a second point of partial obstruction some ten inches distally.

On November 21, 1938, in view of the fact that the obstruction was incomplete, the bulb of the Miller-Abbott tube was deflated and the tube was clamped off. The patient was given fluids and soft diet by mouth. However, within twenty-four hours, he experienced mild but definite cramp-like pain across the upper abdomen. The blood chlorides were 595 mg. per cent; the carbon dioxide combining power was 58.6 volumes per cent.

It was felt that further conservative treatment was futile and accordingly the patient was reoperated on November 29, 1939. Under avertin and ethylene anesthesia, a lower right rectus incision was made and a mass immediately presented itself into the abdominal wound. It was covered by omentum and made up of a loop of intestine bound upon itself. The proximal portion was thickened and almost completely stenotic and about ten inches distally there was another obstruction. An entero-enterostomy was made so as to exclude the involved loop, using chromic for the mucosal sutures and linen for the serosal suture. The abdomen was closed in layers using chromic throughout and skin for the skin.

Following operation, the patient did exceedingly well and the Miller-Abbott tube was withdrawn within five days. The wound healed by primary union. He was discharged on the fourteenth postoperative day.

Case 2. History (Adm. 447094). The patient, a married woman, was first admitted to The Mount Sinai Hospital in January, 1939 with a negative past history except for an umbilical hernia of twelve years' duration which had always been reducible. Ten days prior to admission the hernia had been irreducible for twelve hours. Forty-eight hours prior to entry the hernia again became irreducible, progressively larger, painful and tender. Vomiting ensued. There was obstipation for forty-eight hours.

Examination. The patient was a markedly obese woman; temperature, 101°F.; pulse, 110 per minute; hydration moderate. Crepitant inspiratory râles were heard at the left base. The blood pressure was 130 systolic and 100 diastolic. Beneath the umbilicus was an irregular mass about 20 cm. in diameter, the overlying skin was reddish purple and hot. No peristalsis was seen or heard in the sac; the abdomen elsewhere was soft with borborygmi audible.

Operation (Dr. Druckermer). Immediate operation was performed under 150 mg. procaine (spinal anesthesia). The sac was opened after the hernia ring was defined. The sac contained about two feet of bowel which was congested. There

were two points in the bowel where the bowel entered the sac and returned into the abdomen where the changes incident to strangulation were more marked than elsewhere due to pressure. Circulation rapidly returned except in the two severely constricted points described above. The bowel was temporarily replaced into the abdomen while the operation was continued. Reinspection showed a definite improvement in the two questionable areas and faint peristaltic waves were seen to pass through. The operator felt the bowel to be viable and it was replaced. A typical Mayo hernioplasty was performed.

Postoperative course. Two days following the operation stool and flatus were passed. There was no distention. The patient developed some chest signs which were interpreted as atelectatic and corroborated by x-ray examination of the chest which revealed an elevated right portion of the diaphragm. The patient ran a low grade temperature of undetermined origin although the wound appeared clean. The significance of this temperature will be better evaluated in the light of her second admission. The patient was discharged well and afebrile, twenty-seven days post-operatively.

Follow-up (September 6, 1939). The patient was well and the wound was well healed until two weeks prior to reporting to the Follow-Up Clinic. At that time, there was a spontaneous discharge of a brown, purulent material from the mid-portion of the wound. It was noted that the discharge did not appear fecal and no gas escaped.

Second admission (October 11, 1939). The patient was readmitted to the hospital with a frankly fecal discharge. There were two openings separated by normal skin. In addition, she experienced some epigastric fullness and cramps following meals.

Examination. The abdomen was pendulous. There was a transverse scar in the mid-abdomen in the center of which was an irregular, indurated area with two sinus openings which drained fecal material. Insoluble carmine by mouth appeared on the dressings in four hours. Attempts to heal the fistula without operation consisted of local application of silver nitrate and ultra-violet rays to the area. These forms of therapy proved ineffective. It was felt that some mechanical factor was at work to prevent the fistula from closing as there was no evidence that it was a mucocutaneous type. X-ray studies of the small bowel were undertaken with a Miller-Abbott tube *in situ* (fig. 2). X-ray studies showed enormously dilated loops of small bowel up to the point at which the Miller-Abbott tube could be passed. With the Miller-Abbott tube *in situ* to decompress the bowel the patient was operated upon.

Operation. Avertin and ethylene anesthesia was administered. A transverse incision was made circumscribing the skin around the sinuses which were sewn over. A mass of indurated tissue representing the region of the sinus tract was encountered communicating with the small intestine. The tissues of the abdominal wall were edematous. The abdomen was entered through a transverse incision. Numerous omental adhesions were divided until the excised fistulous tract was defined adherent to the loops of intestines entering into its formation. The Miller-Abbott tube was identified and a tremendously hypertrophied and dilated afferent loop was also identified. The small distal loops were adherent to the sinus tract, all entering a complex mass of numerous fistulae at the apex of the mobilized small bowel. A continuous loop of bowel was then identified, the proximal half extremely dilated, the distal half small and entering the fistulous communication, which, when cut away from the two presenting loops, revealed the following state of affairs: a very small opening in the extremely large loop and two small openings in the distal collapse loop, the two small openings the result of the loop being pulled up in a U-shaped manner. There was complete discontinuity of the bowel except for the small fistulous tracts; and the entire lumen of the bowel had been compromised so that the only openings were the small communications with the skin. The opening in the dilated

proximal loop was closed over and the small distal loop because of two openings was resected into healthy tissue. A lateral side-to-side anastomosis was then done between the dilated afferent and the small efferent loops. A typical Mayo hernioplasty was again done. Drainage was instituted subcutaneously at either angle of the wound. The resected specimen measured 12 cm. in length, showing a moderate circumscribed stricture of the small intestine due to marked fibrosis of the submucosa.

Postoperative course. The patient made a very smooth and uncomplicated recovery. The Miller-Abbott tube proved a valuable adjuvant. It was removed seven days after operation. The bowels moved regularly. There was never any vomiting



FIG. 2. X-ray showing enormous dilatation of the small bowel proximal to the site of stricture. Arrow points to this area.

or any abdominal distention. The wound collected some non-odorous purulent material which necessitated tube drainage but which did not retard her convalescence and she was discharged twenty days after operation. At the present time the wound is well healed and she is asymptomatic.

DISCUSSION

For the most part, the complications arising as the result of intestinal strangulation in hernial sacs are directly in proportion to the degree of mechanical constriction and vascular compromise. These manifest themselves relatively early in the postoperative period if a *restitutio ad integrum* does not occur either as the result of complete viability of the reduced gut

or its removal by the surgeon. Gangrene of the replaced bowel, perforation and peritonitis are the chief causes of early postoperative manifestations and accounts for most of the mortality of this condition, omitting for immediate consideration those patients in whom intestinal resection was primarily undertaken for gangrene. Generally the condition of the intestines as found at operation can be delineated into three groups. In the first, there is no doubt as to the viability of the gut. The hernial sac contains a clear serous fluid and after the constricting ring is cut a slightly hemorrhagic-appearing length of bowel immediately assumes a normal healthy appearance and the points of constriction immediately dilate. In the second group, the intestine is frankly gangrenous, the seat of an advanced hemorrhagic infarction, sometimes actually perforated. In these instances the sac contains bloody fluid; at times malodorous or even frank, foul-smelling pus may surround the intestine which is thin-walled, inelastic and blackish-green in appearance. The mesentery is swollen, ecchymotic, and the vessels may or may not pulsate. No peristalsis is seen passing through the involved portion. Between these two extremes, the obviously viable and the frankly gangrenous, there is a large group in which even the most experienced observer will have difficulty in accurately appraising the viability of the exposed gut. The bowel may appear healthy except for the areas at which the strangulation actually occurs and following long continued observation peristalsis may be judged to be sufficiently active to warrant replacement. In other cases, the color may return to disillusion the operator, resulting in a false sense of security. Attention has been called to the fallibility of the judgment of the surgeon in this respect by Beller and Colp (1) who reviewed 278 cases of strangulated herniae and found that fourteen deaths in this series occurred with symptoms suggesting gangrene of the replaced bowel in a group of forty-seven patients in which the operative note suggested some doubt in the operator's mind as to viability. In eight of these cases, autopsy substantiated the clinical impression. Fortunately, not all cases in which the extent of bowel damage has been underestimated go on to gangrene. Although complete devitalization does not occur, the changes occurring in the bowel as the result of strangulation particularly at the points of constriction (Schnürfurche) do not permit a return to normal. The mucosa of the bowel, the most vulnerable element, undergoes necrosis. The ensuing ulceration combined with infection and diminished blood supply as the result of local thrombosis results in a failure of mucosal regeneration. Fibroblastic replacement results in stricture which may be either tubular involving a variable length of intestine or anular involving only the areas actually strangulated. Ginzburg and Klein (2) have reviewed five such cases and call attention to the time interval between replacement of the damaged bowel and the development of a sufficiently narrow bowel lumen to give rise to symptoms of either complete or partial intestinal obstruc-

tion. Our first case was unusual in that the train of obstructive symptoms with tubular stenosis occurred only three weeks after the original herniotomy. In our second case nature had almost effected spontaneous enterectomy, the involved bowel undergoing perforation which fortunately became adherent to the incision, resulting in a fecal fistula. The continuity of the bowel in this case was almost completely interrupted, the point of egress of the intestinal contents being narrowed beyond recognition so that an almost blind loop of the small intestine was encountered at operation. The first manifestations of bowel damage in this case occurred as late as nine months after the initial operation. In both cases marked intestinal obstruction as determined by X-ray with the aid of the Miller-Abbott tube was an outstanding feature. In the first case, clinical symptoms of obstruction were predominant; in the second case, the symptoms were altered by the development of a fecal fistula which mitigated the obstructive phenomena, which were nevertheless present. In both cases, short-circuiting operations were employed to correct the condition. In the second case, an enterectomy had to be resorted to because of the numerous fistulous openings and the strictured condition of the involved loop.

SUMMARY

1. Two unusual cases of late intestinal complications following herniotomy for strangulated hernia are presented.
2. In both instances intestinal stenosis was the underlying pathological process.
3. In one case a fecal fistula developed as late as nine months after herniotomy on this basis.
4. Intestinal obstruction was the predominant clinical feature in both cases.
5. Short-circuiting procedures were employed in both cases to effect a cure. In one case an enterectomy had to be performed.

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EXTRADURAL VARIX SIMULATING HERNIATED NUCLEUS PULPOSUS

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In many cases after the disclosure at operation of an extruded nucleus pulposus, the clinical course and picture can be reconstructed from the anatomical location of the lesion. Beginning with the history of trauma, continuing with the onset of pain in the lumbar region radiating down the outer aspect of one leg, we note the absence of an ankle jerk and slight sensory changes in the distribution of the fourth or fifth lumbar nerve root, and finally obtain cerebrospinal fluid with elevated total protein. There may be any number of deviations from this classical picture. The history of trauma may not be obtained; the reflex or sensory changes, or both, may be absent; the protein content of the cerebrospinal fluid may be normal. There finally remains but one constant feature, that is, pain. But even this may not follow the usual distribution. It may not descend below the knee. Any or all these variations may be encountered in a protruded disc at the common site, lumbar 4 or 5.

There is little wonder that in the atypical cases, confirmatory evidence by air myelography or spinal lipiodol studies assumes an important role. The need of this confirmation is especially called for when (in the absence of reflex changes) the sensory findings are misleading. A clear cut sensory level, as obtained in many spinal cord tumors, is readily determined, but even the most cooperative and intelligent patient can lead the examiner astray in an examination to determine sensory changes. Possibly this class of patients is too eager to help. Those who are not cooperative or who belong to a lower order of intelligence, offer difficulties from an obviously different angle.

Based upon a rather typical history and lipiodol x-ray pictures, a pre-operative diagnosis of herniated nucleus pulposus was made in the patient whose case report follows.

CASE REPORT

History (Adm. 406437). A. S., a fifty-four year old married woman, was examined by Dr. Israel Strauss in March, 1937. She had been under observation in November, 1936 and in January, 1937 for the same complaint, namely, pain in the lumbar region and left leg. Some nine years prior to the onset of the pain, she had injured her back by a fall while skiing and had spent three days in bed. For a year prior to her first admission, she had noted pain in the lumbar region just to the left of the midline. The pain was aggravated by stooping. She also had pain in the left thigh and knee. This was a separate complaint, as there was no radiation of pain from the back to the

leg. On the first admission one observer noted diminished sensation up to the tenth thoracic dermatome with sparing of sacral segments. The left knee jerk was slightly more active than the right, and the proximal muscles of the left lower extremity seemed weak. The x-ray examinations of the spine were negative. The cerebrospinal fluid studies showed no block and a normal protein content.

During a two months' period the patient wore a brace and received radiotherapy to the back without relief. When she was readmitted there was noted the same difference in the knee jerks. This time the sensory changes were limited to hypalgesia over the outer portion of the left thigh in the distribution of lumbar two and three.



FIG. 1. Lipiodol defect at fourth lumbar interspace

The lipiodol which was injected into the cisterna magna descended promptly to the cul-de-sac. When the patient was in an inverted position the lipiodol would not flow up past the fourth lumbar vertebra during the half hour in which it was observed. Most of the lipiodol was washed out and the patient was discharged.

Two months later the patient was readmitted. In the interim her pain had increased. Walking was all but impossible; rising from a sitting position gave excruciating pain. Lipiodol was again injected and this time was interpreted as showing a narrowing and asymmetry at the fourth lumbar interspace (fig. 1).

Operation. On April 1, 1937 a laminectomy was carried out from lumbar two to lumbar four. When the dura was opened, the fourth lumbar root on the left could be seen stretched over and elevated by a soft bluish swelling. Under the mistaken

idea that this was a herniated disc, an incision was made in the anterior dura into the mass. Very brisk venous bleeding ensued. It was controlled by cotton until a muscle graft could be used which completely controlled it.

Immediately upon reacting from the anesthetic, the patient found that her pain had disappeared. She has remained well to date.

DISCUSSION

Last year before the New York Surgical Society, Dr. Jefferson Browder reported a somewhat similar case. Recently, Dr. James Greenwood, Jr. of Houston, Texas had an excellent exhibit at the American Medical Association meeting of seven cases showing spinal epidural varicosities at various levels, two of which were in the lumbar region and clinically resembled herniated discs. I know of no other reported case. In their very complete paper, Globus and Doshay (1) make no mention of the particular lesion under discussion. The epidural hemangioma are of course thoroughly dealt with.

If the existence of such a lesion is borne in mind, its true character should be diagnosed once it is exposed. As suggested by Greenwood, it is probably best treated by electrocoagulation.

SUMMARY

1. Attention is called to the condition of varicosities in the extradural spinal veins.
2. In the lumbar region this may resemble the clinical picture of a herniated nucleus pulposus.

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INTERSTITIAL HERNIA

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"An interstitial hernia is one that in its development does not follow the course of the spermatic cord into the scrotum, but spreads out in the interstices or planes of the abdominal wall itself," (Moschcowitz (2)). Three varieties of interstitial hernia are recognized anatomically: 1) inguino-superficial, in which the sac lies between the aponeurosis of the external oblique and the skin; 2) interparietal, in which the sac lies in the fascial or muscular planes of the abdominal wall, and 3) properitoneal, in which the sac lies between the peritoneum and the transversalis fascia. Many of these hernias are bilocular, one loculus being an indirect hernial sac which communicates at its neck with the interstitial hernia. Although interstitial hernias are uncommon, Lower and Hicken (1), in 1931, found that 589 cases had been reported in the literature. A few cases have been reported since then.

The following are the records of two cases of interstitial hernia for which operation was performed.

CASE REPORTS

Case 1. History (Adm. 460002). S. G., a man, age 27 years, was admitted to the hospital on July 18, 1940, with the complaint of a left inguinal hernia of four years' duration. The hernia was not completely reducible for many months. The left testis was undescended since birth.

Examination. There was a large, irreducible, left inguinal hernia (fig. 1). A well developed left testis was undescended, and could be felt high up in the upper portion of the inguinal region within the hernial bulge. The left side of the scrotum was poorly developed. The blood Wassermann reaction and urinalysis were negative.

Operation. Gas, oxygen, and ether anesthesia was administered and a left inguinal incision made. A large peritoneal sac measuring about ten by six centimeters in diameter presented immediately under the subcutaneous tissue lying on the external oblique aponeurosis. The sac was isolated from the surrounding subcutaneous tissues. During this procedure there was a sudden diminution in the size of the sac, as though some of its contents had been reduced. The sac was found to come out of the external ring and turn upward between the skin and the external oblique aponeurosis. The latter was divided. A large portion of the hernia was found in the inguinal canal in the usual relation to the cord structures. On opening the sac, the testis was found in its upper part. It measured about three by two centimeters in diameter, and was of normal consistency. Some omentum presented through a very wide internal ring.

The sac was isolated from the cord structures. When the neck of the sac was exposed, the sigmoid colon was found to form a part of the posterior wall of the sac

(sliding hernia). An attempt to construct a new peritoneal mesentery at this site was partially successful. The wide neck of the sac was closed with a continuous silk suture. Strands of connective tissue between the vessels of the cord were divided to allow lengthening of this structure. The testis was sufficiently mobilized to place it in the scrotum without tension. The conjoint tendon of the internal oblique and transversalis fascia and the external oblique aponeurosis were united to Poupart's ligament over the cord with interrupted silk sutures. This was followed by an overlap of the remaining leaf of Poupart's ligament.

Postoperative course. During the first postoperative day the temperature rose to 103°F. This was associated with some cough, cyanosis and dyspnea. There were signs of an atelectasis of the right lower lobe. The patient was placed in an oxygen tent for two days. On the fourth postoperative day the temperature was normal and the pulmonary signs had disappeared. The wound healed by primary union. There was no enlargement of the testis. The patient was discharged 16 days after operation.



FIG. 1. Preoperative photograph of inguinal regions; circle indicates site of left testis.

Follow-up course. Examination on September 17, 1940 showed a firmly healed wound. The left testis, of normal size, was located in the scrotum (fig. 2).

Case 2. History (Adm. 441677). J. G., a man, age 54 years, was admitted to the hospital on June 8, 1939, with the complaint of a recurrent, right inguinal hernia of three years' duration. A hernioplasty was performed at another hospital six years before admission. A recurrence was noted three years after operation. The patient wore a truss after the detection of the recurrence.

Examination. There was a large, recurrent, right inguinal hernia filling the right inguinal region and scrotum. The hernia was directly under the skin and extended upward in the abdominal wall well above the site of the internal inguinal ring.

Operation. Avertin, ethylene anesthesia was administered and a right inguinal incision was made, excising the old scar. After incising a thin layer of scar tissue, a very large sac measuring about eight by four inches in diameter was exposed. The wall of the sac was thin, and many loops of small intestine could be seen through it. The sac extended from about two inches above the internal ring into the scrotum.

The hernia was indirect and direct, the latter component coming through a large defect in the floor of the inguinal canal. The absence of any adequate barrier permitted the sac to bulge through the small amount of scar tissue to present under the skin. When opened, the sac was found to contain many feet of loops of small intestine. The intestinal loops in the scrotum were adherent to each other in many places with many areas of constriction of the intestine. These adhesions were divided so as to straighten out the intestinal loops. The raw surfaces were peritonized.

After all the intestinal loops were reduced into the peritoneal cavity, the neck of the sac was found to be rather rigid, measuring about six by three centimeters in diameter. The neck of the sac was closed from within with a continuous silk suture. The sac was divided low down in the inguinal canal, removing the inguinal portion and not disturbing the scrotal portion. In order to facilitate repair, the cord structures were divided at the internal ring and partially excised. The aponeurosis of the external oblique at the inner margin of the defect in the direct space was united



FIG. 2. Postoperative photograph of inguinal regions

to Poupart's ligament with interrupted silk sutures, followed by an overlap of the remaining leaf of Poupart's ligament. The skin was closed with interrupted silk sutures.

Postoperative course. A fairly large amount of serosanguinous fluid collected in the large dead space in the operative site. This fluid subsequently became infected, necessitating irrigations through a small opening in the wound. There was slight fever for a period of three weeks. The patient was discharged with a healed wound 25 days after operation.

Follow-up course. Examination on March 19, 1940 showed a firmly healed wound.

COMMENT

Both patients had the inguinoperitoneal variety of interstitial hernia. The first case, like the majority of cases of this type, was associated with an undescended testis. In the series of 123 cases collected by Lower and Hicken (1), 86 were in males. Ectopic testes were present in 67 of these cases. The undescended testis is not a constant factor, because in some

instances the testes are in their normal position, and in some cases the condition is found in females. The hernia in the second case was anatomically in the group of inguinoperforic hernias, but the condition was artificially produced as a result of the previous operation.

Of aid in the diagnosis of interstitial hernia is the association of a hernia extending above the site of the internal ring, an ectopic testis, and symptoms of intestinal obstruction. The latter was not present in the cases reported. In some instances a hernia may not be palpable, the testis may be in the scrotum, and no obstructive symptoms are present. The surgical treatment of the non-strangulated cases is easily carried out if the condition is properly recognized.

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ASYMPTOMATIC TRAUMATIC DIAPHRAGMATIC HERNIA MISTAKEN FOR PULMONARY TUBERCULOSIS

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[From the Surgical Service of Dr. Harold Neuho]

Since the advent of contrast radiography of the gastro-intestinal tract, the correct clinical diagnosis of diaphragmatic hernia has been made more frequently. In 1854, Bowditch (2) made the first diagnosis of diaphragmatic hernia during life. Arnsperger (1) stated that the condition had not been recognized clinically more than ten times prior to 1908. In 1912, Giffin (4) collected 690 cases from the literature, but only fifteen of these had been diagnosed before death. Kienböck (8), in 1913, noted that in the German literature only three cases had been diagnosed clinically and proven by autopsy.

With the use of gastro-intestinal x-ray examination, the condition is now recognized more frequently. Hundreds of cases have been described in the literature and even the public has become surprisingly well aware of its existence, due to the newspaper notoriety afforded the "upside down stomach." Harrington (5) reported that at the Mayo Clinic, only thirty cases had been recognized clinically in the twenty-five year period prior to 1925. Of these nineteen were operated upon. On the other hand, in the twelve years from 1925 to 1937, two hundred and eleven cases were diagnosed, and one hundred and thirty-one of these were treated surgically (6).

A diaphragmatic hernia may be entirely asymptomatic and only discovered upon routine physical examination or at post-mortem. Usually it gives rise to symptoms, which simulate organic disease of the upper abdominal organs or the thoracic viscera. Harrington, in reporting one hundred and five cases, stated that an average of three erroneous diagnoses were made before the correct one was determined. Furthermore, nineteen of these patients had had unnecessary laparotomies. He advocated the inspection of the diaphragm in all upper abdominal operations, if pathological lesions are not found in the viscera.

Aside from presenting symptoms suggestive of upper abdominal disease, the displacement of the abdominal organs into the thoracic cavity may simulate disease of the lungs or of the heart. Hedblom (7), Truesdale (13, 14) and others have stressed the importance of considering herniation through the diaphragm in the differential diagnosis of obscure thoracic symptoms. A review of the literature reveals a number of instances in

which patients have been treated for pulmonary tuberculosis, when the symptoms were actually due to a diaphragmatic hernia.

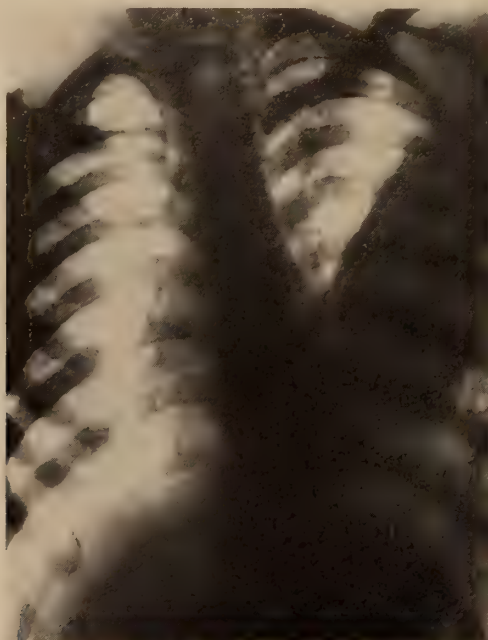


FIG. 1. X-ray examination revealed a large shadow in the left thorax

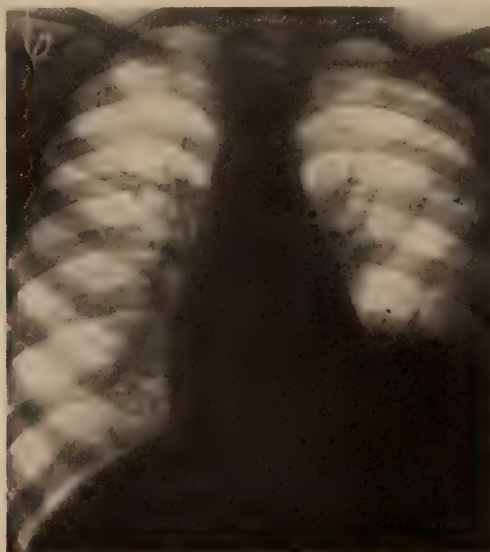


FIG. 2. After a period of observation for two years, the shadow in the left thorax cleared, but x-ray examination still revealed some pathology at the left base.

Truesdale, in 1935, reported the occurrence of a traumatic diaphragmatic hernia in a boy of five, which had been diagnosed by a number of

eminent clinicians as pulmonary tuberculosis. Paiseau, Guenaux and Gautier (11) cited a case in a child, who was erroneously treated for tuberculosis of the right lower lobe. Later, lipiodol bronchography and gastrointestinal studies revealed the presence of a diaphragmatic hernia. Morton (9) reported the case of a five year old boy, whose x-ray was interpreted as a pulmonary lesion until later investigation showed the presence of abdominal contents within the thorax. Truesdale, in 1939, operated upon a girl of ten, who had been sent to Colorado eight years previously because of the diagnosis of pulmonary tuberculosis.

Badenhauer (cited by Bowen (3)) performed the first laparotomy for a hernia of the diaphragm (1879). The first transthoracic operation for diaphragmatic hernia was performed in this country by O'Dwyer (10) in 1889. During the removal of a piece of rib for drainage of a supposed



FIG. 3. X-ray examinations taken six months after operation revealed a normal chest with a slightly elevated left diaphragm.

empyema, he discovered the stomach and intestines in the thorax. He reoperated the next day and repaired the hernia but the child died a few hours after operation. In the same year Postempski (12) reported the transthoracic repair of a diaphragmatic hernia.

The case presented here, is unusual because an erroneous diagnosis of pulmonary tuberculosis was made in an asymptomatic child during a routine investigation of his family. His father had a chronic rheumatic lesion of the mitral valve and was also suspected of having tuberculosis. X-ray examination of the child's chest revealed a large shadow in the left thorax (fig. 1).

The boy was kept under observation for two years in hospitals and clinics during which time the shadow cleared, but x-ray examination still revealed some pathology at the left base (fig. 2). Aspirations were done on numer-

ous occasions without success, until gastric contents were finally obtained and the correct diagnosis established. It is of interest that while the boy was under observation, his father died without definite evidence of ever having had pulmonary tuberculosis. The boy was operated upon and cured. X-ray examinations (fig. 3) performed six months after operation revealed a normal chest with a slightly elevated left diaphragm.

CASE REPORT

History (Adm. 324137). A white boy, eleven years old, was admitted to The Mount Sinai Hospital on March 21, 1931. The patient had no symptoms and did not feel ill. In 1927, following an automobile accident, the patient spent six months in a hospital. In 1929, two years prior to admission, because of suspected tuberculosis in his father, the child was examined at a clinic. Thereafter, he visited the clinic once a week. Following a fluoroscopic examination some time later he was admitted to another hospital where he was kept in bed for two months. During this time a diagnosis of "pneumothorax" (according to the family) was made and aspiration of the chest was attempted without success. Otherwise, the past and familial history is irrelevant.

One month after discharge, he was sent to another hospital in Atlantic City for convalescent care. He remained there ten weeks. After discharge from that hospital he again visited a clinic at weekly intervals and at his last visit a small amount of white fluid was aspirated from the left lower chest. Following this procedure he was advised to enter The Mount Sinai Hospital.

The patient's only symptoms consisted of slight dyspnea and palpitation. He was slightly underweight but had no cough, expectoration, or chest pain. He felt strong and had a good appetite.

Examination. The only positive findings related to his chest. There was lagging of the left side of the chest on deep inspiration. The right hemithorax had normal resonance and breath sounds throughout. Over the left lung, there were diminished resonance, diminished breath sounds and vocal fremitus from the seventh rib down posteriorly. Occasional râles were heard over this area. The left apex was clear. A tympanic note could be elicited in the posterior axillary line about the eighth rib.

The right border of the heart could be percussed three centimeters to the right of the mid-sternal line. The rate was regular, and the sounds were of good quality. A slight systolic murmur was heard at the aortic area.

Urine examination and other laboratory tests were all essentially negative.

Examination of the gastro-intestinal tract on March 30, 1931 showed the larger part of the stomach in the left chest. The stomach was inverted so that the cardiac end pointed downward and the pyloric end upward. Aside from the displacement there was no organic lesion present in the stomach or duodenum. Gastric tone and peristalsis was normal. Gastric motility was not delayed. Six hours after eating, the stomach was empty. Observations six, eight and twenty-four hours after meals showed the splenic flexure to be situated above the diaphragm and in the left chest. X-ray examination showed the presence of a diaphragmatic hernia, and operation was performed on April 3, 1931.

Operation (Dr. Harold Neuhof). Thoracotomy and transpleural repair of a left traumatic, diaphragmatic hernia was performed under nitrous-oxide, oxygen and ether anesthesia.

A long intercostal incision was made in the seventh interspace. When the pleura was opened, omentum was noted first and it was thought that the peritoneal cavity had been entered. However inspection below showed that the exposure was above the diaphragmatic limits. The lung was not seen at first. The pleural cavity was

occupied by stomach, loops of small intestine with omentum, spleen and splenic portion of the large intestine. The left lobe of the liver was also in the chest cavity. There was no covering to these viscera in the sense of a sac, and the traumatic nature of the lesion was thereby confirmed. The stomach and other viscera were introduced into the abdomen without difficulty and the site of the defect thereby exposed.

The defect was oval, about three by two by one inches, and was situated directly to the left of the pericardial attachments. It was situated in the tendinous part of the diaphragm, but the major portion of its left lateral rim was composed of muscular tissue. The left lateral aspect of the stomach was also incorporated in the left lateral rim. Apparently this defect followed the injury, at which time it is assumed that a probable tear in the wall of the stomach led to the attachment of the raw area to the torn edge of the diaphragm. Anteriorly and posteriorly the rim was free. On the right lateral aspect, the left lobe of the liver was incorporated in the margins of the defect. This, however, was not a pathological process but represented the site where normally extraperitoneal liver is incorporated with the under surface of the diaphragm. The peritoneal part of the left lobe of the liver was normal.

A rim was present anteriorly, posteriorly and to some degree laterally, but not mesially. The lung was collapsed and atelectatic with a few adhesions between the border of the lower lobe and the edge of the diaphragmatic defect. Similarly there were a few adhesions between the external aspect of the pericardium and the diaphragmatic defect. An interesting feature was the rapid aeration of the atelectatic lung, except for a thin strip at the inferior portion. Intranasal pressure inflation was used in order to reexpand the lung.

The free margins of the defect were held with Allis clamps, after the abdominal contents had been reduced and held in place. Adhesions of the lung and the pericardium were severed and suturing of the defect was begun anteriorly. This did not make for satisfactory closure and was discontinued. The few sutures that had been passed were removed, and suturing was begun posteriorly directly adjacent to the esophagus. A few sutures were placed to narrow the defect. Incision was then made to free the gastric attachment so that sutures could be passed through the left lateral rim without traversing the stomach. These sutures were passed mesially through the thinned tendinous portion of the diaphragm, including the liver substance in them, and laterally through the free margin of the defect where the stomach was attached. The margins were approximated without tension.

The anterior part of the closure was very simple, because the diaphragm was free in that region. Wide grasping of the mesial portion was not possible because of proximity to the pericardium. A fascial graft for reenforcement would have been impossible, inasmuch as its mesial portion would have had to be attached to the pericardium. The suture appeared adequate to close the defect without tension. The lung was inflated. Pericostal sutures of stout chromic gut were inserted, followed by layer closure of the musculature and skin. Underwater drainage by catheter was established in order to permit escape of air from the pleura.

Postoperative course. Following operation the temperature ranged between 101° and 102°F. for ten days and then returned to normal. The catheter was removed from the pleura after twenty-four hours and the wound healed by primary union.

X-ray examination of the chest on April 20, 1931 showed a small area of pneumothorax at the left base with a small pleural effusion. X-ray examination of the gastro-intestinal tract on April 24, 1931, showed the stomach to be situated entirely below the diaphragm. It had normal gastric tone and peristalsis. There was no abnormality noted in the duodenal bulb. Six hours after meals, there was a small residue in the stomach. The small intestine and colon were situated normally.

Recovery was uneventful. The patient was discharged on May 10, 1931.

Follow-up examination of the chest by x-ray examination on June 22, 1931, showed a thickened pleura at the left base with moderate elevation of the left diaphragm. Since

the last examination the pleural effusion previously noted had entirely disappeared. Reexamination of the gastro-intestinal tract on July 3, 1931, showed the stomach to be below the diaphragm and in normal position. Gastric tone, peristalsis and motility were normal. No abnormality was noted in the duodenal bulb.

On December 5, 1932, the patient was again seen and found to be in perfect health, with no symptoms relative to his previous operation. A report from his physician in May 1940, states that he is perfectly well, with the diaphragm in normal position.

COMMENT

A case of asymptomatic diaphragmatic hernia is presented. During a routine examination of a family suspected of being tuberculous, this child's x-ray was interpreted as pulmonary tuberculosis. The child was kept under observation for this disease for two years. Only when a "fortuitous" chest aspiration revealed gastric contents was the correct diagnosis made. Transthoracic repair of the hernia resulted in a complete cure.

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COMPLETE DIVISION OF THE SPERMATIC CORD IN CONJUNCTION WITH INGUINAL HERNIOPLASTY

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The efficacy of any one of the numerous procedures for hernioplasty has usually been judged by the "recurrence rate" of that procedure. Theoretically and practically, the point of egress of any structure at the peritoneal reflection is a potential source for recurrence. Moschcowitz (1) stressed this point in his monumental monograph on hernia:

"Assuming the theory to be correct that the transversalis fascia is the sole important structure needed to retain the viscera within the abdomen it becomes manifest that in order to cure a hernia, the only procedure necessary is to close the hole in this fascia. Unfortunately this is impossible in the majority of herniae because of the importance of blood vessels which pass through this hole. The conclusion follows that a radical cure of the most frequent forms of hernia, namely, oblique inguinal and femoral, is entirely impossible in the strictest anatomical sense, because no matter what we do, the hole in the transversalis fascia through which the spermatic or femoral vessels pass, still remains. We may dislocate the hole, we may make a new exit for these vessels but the hole is still there. In practice, however, we find that the surgeon gets around the difficulty although he must ignore the weak spot in the transversalis fascia, by fortifying this hole, building a buttress of fascial or muscular structures in front of the opening."

If this were so, it would seem that with the spermatic cord out of the way, the recurrence of an inguinal hernia could be kept at a minimum. This would be true especially in those cases in which one or more operations for the cure of the hernia have been failures. Moschcowitz (1) and others, however, have felt that complete division of the spermatic cord meant the sacrifice of the testis. In his discussion on the causes of failure of hernioplasty, Moschcowitz stated:

"On theoretical grounds no inguinal hernia is curable unless the testis is sacrificed; as long as an opening be left for the escape of the spermatic cord through the transversalis fascia, there remains a weak area through which a recurrence becomes possible."

However, the experimental and clinical evidence gathered and presented recently by Neuhoﬀ and Mencher (2) showed that division of the entire spermatic cord between the internal and external abdominal rings with retention of the testis does not necessarily lead to atrophy of this organ.

In over two-thirds of the cases reported by them in which complete cord severance was employed little or no atrophy occurred. The blood supply to the testis is adequate because potential collateral circulation exists among the deferential, the internal spermatic and the cremasteric arteries. This circulation is present on each side of the scrotum and communicates with the same system on the other side through the scrotal arterial system.

Burdick and Higenbotham (3) have reported cases in which no atrophy occurred after complete severance of the cord. Their series as well as the one reported by the author (2) are the only recorded groups of cases in which division was employed as part of the hernia operation. Burdick and Higenbotham stated that the "recurrence rate" was 11.8 per cent in the entire group. The highest "recurrence rate" was noted in the group of "recurrent" hernia, 23.7 per cent. This high rate is somewhat surprising since it is only slightly smaller than the rate of recurrence (about 30 per cent) in those "recurrent" cases in whom no division of the spermatic cord was done. In the authors' series, no recurrences took place in this group.

In this series, the procedure of complete division of the spermatic cord was carried out in twenty-four cases as part of the hernioplastic procedure. In all cases division of the cord was performed on one side only. There were no deaths. The types of hernia are listed as follows:

	<i>cases</i>
Direct inguinal hernia.....	2
Indirect inguinal hernia.....	3
Recurrent hernia.....	9
Direct—indirect hernia.....	5
Bilateral hernia.....	4
Sliding hernia.....	1
	<hr/> 24

It should be noted that most of the cases were of the older age group and that the hernias were not small and not of the simple type. In comparing the results, therefore, with those of other types of procedures this point must be taken into consideration.

Of the twenty-four cases, six were unavailable for further observation. Eliminating these six cases, there remain for consideration eighteen cases which were observed over a period varying from six to fifty-five months.

In this series, only two hernias recurred. One hernia was of the direct-indirect type and the other was of the bilateral type on one side in which division of the cord had been performed on the same side. This represents a recurrence rate of eleven per cent for the entire group.

It is of interest to note that in the nine cases that had had previous hernioplastic procedures, there was no recurrence following division of the cord and hernioplasty. This is in sharp contrast to the results reported by Burdick and Higenbotham.

This small series of cases substantiates the theory that in inguinal hernia,

if the cord structures could be eliminated, the recurrence of hernia should be at a minimum since a more effective hernioplastic closure and buttressing of the abdominal wall is possible.

Indications for division of the cord with hernioplasty. The procedure of division of the spermatic cord in conjunction with hernioplasty is definitely indicated in the recurrent type of hernia in old people. It is also indicated in younger individuals in whom one or more previous procedures had been failures and in whom, from the local appearance of the anatomical structures, recurrence might take place again.

In older individuals with large scrotal hernias and with wide necked sacs, the procedure should be considered.

The technique of severance of the cord is simple. Each structure of the cord is tied off by separate suture and the division is made between the internal and external abdominal rings. Division in the scrotum, at or below the external ring, may destroy collateral circulation. Careful aseptic and hemostatic technique is essential since hematoma or infection dissecting all the planes into the scrotum will compress the collateral circulation to the testis.

This procedure should not be employed in those cases in which malde-scended testis is associated with hernia. The circulatory apparatus in these cases is variable and the presence of adequate collateral circulation might be questionable.

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PUNCTURE OF THE EXTERNAL ILIAC ARTERY AND VEIN DURING INGUINAL HERNIOPLASTY

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Traumatic perforation of the external iliac artery and vein during inguinal hernioplasty is unusual. The purpose of this report is to present an illustrative case and the immediate management of the surgical accident.

CASE REPORT

History (Adm. 400224). M. S., a male patient, 20 years old, was admitted to the hospital on October 26th, 1936 for the repair of a right indirect inguinal hernia. His past medical and surgical history was not significant. For five years prior to admission the patient had noted a bulge in the right groin which had gradually increased in size but had never descended into the scrotum. The only complaint was a dull ache in the right inguinal region which occurred after physical exertion.

Examination. Except for the local condition, the physical examination was negative. There was a hernial mass in the right inguinal canal which descended through the external inguinal ring when the patient strained.

Operation. On October 27, 1936 a modified Andrews-Bassini hernioplasty for right indirect inguinal hernia was performed under avertin gas-oxygen-ether narcosis. A four inch right inguinal incision was made and the external oblique aponeurosis was split in the direction of its fibers. A small indirect sac was identified and dissected up to the internal ring where it was transected with a suture and amputated. Repair was then accomplished by suturing the external oblique aponeurosis and some of the underlying conjoint tendon to the shelving edge of Poupart's ligament. Two such sutures were placed. As the third suture was being placed through the shelving edge of Poupart's ligament, active bleeding was encountered. The suture was removed and an attempt made to clamp the bleeding vessel. This failed, however, because the bleeding came from beneath Poupart's ligament. It became evident that a large vessel had been injured because of the fact that the flow of blood was very profuse and could only be controlled by digital pressure. After bleeding had been checked by pressure, Poupart's ligament was split at right angles to its fibers. The bleeding was then seen to arise from the external iliac artery. There was also additional bleeding from the external iliac vein. This was readily controlled by the use of several fine silk sutures passed through the wall of the vein. A tape was then placed around the external iliac artery and the bleeding from the vessel was controlled in this manner. Several fine black silk sutures were then placed through the wall of the vessel at the site of the small puncture-like perforation. The tape was then slowly released and there was no evidence of bleeding from the previous wound in the vessel. The incision of Poupart's ligament was closed and several Bassini sutures were used to approximate the external oblique aponeurosis and the conjoint tendon to the shelving edge of the inguinal ligament. An overlap suture was then passed, the spermatic cord transplanted subcutaneously, and the skin was

closed with pincettes. When digital pressure was maintained on the bleeding artery, the dorsalis pedis and posterior tibial vessels did not pulsate and the foot and leg on that side assumed a dusky hue. Shortly after the external iliac artery had been sutured and the tape had been removed, pulsations in both the dorsalis pedis and posterior tibial vessels reappeared and the color of the limb appeared to improve.

Postoperative course. About eight hours after operation, the right foot was dusky and the peripheral pulses were feeble on the affected side. On the following day the right foot was normal in color and felt warm. Excellent pulsations were present in the dorsalis pedis and posterior tibial arteries. A hematoma was evacuated on the fourth postoperative day, following which there developed a mild wound infection. The wound was packed down to the fascia with iodoform gauze and the infection



FIG. 1. Infra-red photograph of right inguinal region

readily controlled in this manner. At the time of discharge from the hospital on November 18, 1936 (22 days after operation), the inguinal wound was healed and examination of the right lower extremity was entirely negative.

Follow-up. On March 2, 1937 (5 months after operation), the patient presented himself at the clinic. He complained of slight swelling of the right leg after walking. Excellent arterial pulsations were present throughout the right lower extremity. The circumference of the right leg and thigh was one inch greater than the opposite side. The wound was solidly healed. When the patient was seen on subsequent follow-up visits in September 1937, December 1937, and November 1938 (2 years postoperatively), his subjective complaints were the same, but his physical examination remained essentially negative. At his last follow-up examination in February 1940 (3 years and 3 months after operation) he still complained of slight swelling of

the right leg and foot. Measurements and oscillometric readings made at this time were as follows:

	INCHES	OSCILLATIONS
Thigh		
Right.....	21.5	4-5
Left.....	20	5-6
Calf		
Right.....	15.5	3-4
Left.....	14.5	2-3

There was no edema of either the right leg, ankle or foot. In the region of the right inguinal scar, which was firm, there was a rather extensive dilatation of the superficial veins. No bruit could be felt or heard. The extent and distribution of these dilated veins is illustrated (fig. 1).

DISCUSSION

The course and relations of the external iliac artery are as follows: "The external iliac artery extends from a point opposite the sacro-iliac joint, at the level of the lumbo-sacral articulation, to a point below the inguinal ligament (Poupart's), midway between the anterior superior spine of the ilium and the symphysis pubis, where it becomes the femoral artery" (1). The two main branches are the inferior epigastric and deep circumflex iliac artery both of which arise just above the inguinal ligament. The opportunity for injuring the external iliac artery and its accompanying vein (which lies to its medial side) occurs when Bassini sutures are passed through the mid-portion of the shelving edge of Poupart's ligament. In view of the proximity of these large vessels, it is surprising that they are not injured more frequently. Good visualization and the use of non-cutting needles are both important in preventing this accident. Whenever excessive arterial bleeding occurs while the sutures are being passed through the inguinal ligament, perforation of the external iliac artery should be suspected. Prompt division of Poupart's ligament at right angles to its fibers is indicated in order to control bleeding and to preserve the blood supply to the affected limb. After hemostasis has been accomplished by arterial suture, reconstruction of the inguinal ligament will result in a satisfactory anchorage for the Bassini sutures. The division of Poupart's ligament should in no way influence the final plastic result.

SUMMARY

The case reported here illustrates in detail a punctured wound of the external iliac artery and vein during an inguinal hernioplasty. A brief resumé of the regional anatomy is given. Suggestions are made concerning the prevention, recognition and immediate care of this condition.

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DIRECT HERNIA IN THE FEMALE

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Although inguinal hernias of the indirect type are commonly seen in women, those of the direct variety are encountered but rarely. Several surgeons of long experience admit having never seen a direct inguinal hernia in the female while most of the surgical textbooks consider the condition so much of a rarity as to dismiss the subject with mere passing mention. Stone, for example, in his article on Hernia in Lewis' System of Surgery (12) fails even to mention the occurrence of direct hernia in women, while Homans (1) claims that direct hernia exists only in the male. Murray in his textbook, published in 1910 (11), stated that "inguinal hernia in the female is almost always of the oblique variety. I have never," quoted Murray, "seen a direct inguinal hernia in a woman." Erdman (2) states that for all practical purposes direct hernia may be said to occur only in the adult male, for less than 1 per cent of all direct hernias occur in women. Andrews and Bissell (3) excluded women entirely from their discussion of direct hernia because "its rarity in them is extreme." Christopher (13) similarly disposes of this subject with the statement that "direct hernia is practically unknown in the female."

Recently, in the private practice of the senior author (H. N.), a woman was operated upon for the purpose of repairing a suspected indirect inguinal hernia, but a hernia of the direct type was found instead. The rarity of this condition was remarked upon and the ensuing discussion led to an investigation of the subject.

The common occurrence of indirect, or oblique, inguinal hernia is understandable when we consider that a ready-made cleft in the abdominal wall already exists in the male due to the passage of the spermatic cord from the abdominal cavity into the scrotum and, in the female, to the analogously situated round ligament of the uterus. In addition the precursor of a hernial sac is already present in fetal life as a peritoneal pocket, the so-called vaginal process. Normally, this process is entirely obliterated before birth (except for that portion which becomes the tunica vaginalis testis), but varying portions of this peritoneal pocket may persist into the post-natal period to provide a potential hernial sac.

Direct hernia, on the other hand, does not owe its existence to any preformed breach in the abdominal wall. It makes its appearance when a relatively weakened or unprotected portion of the abdominal wall gives way before the pressure of the intra-abdominal contents. Thus it is

generally taught that direct inguinal hernias tend to occur in middle-aged men whose abdominal muscles and fascial structures have gradually become weakened and thinned out by a lifetime of physical labor; and we are also told that additional factors, such as prostatic urinary obstruction and chronic constipation, hasten the development of this type of hernia by tending to increase the intra-abdominal pressure (1). Malnutrition, too, favors its development. That these factors do not tell the entire story is evident, however, from the fact that direct hernias are practically never seen in ill-nourished and hard-working women who theoretically possess

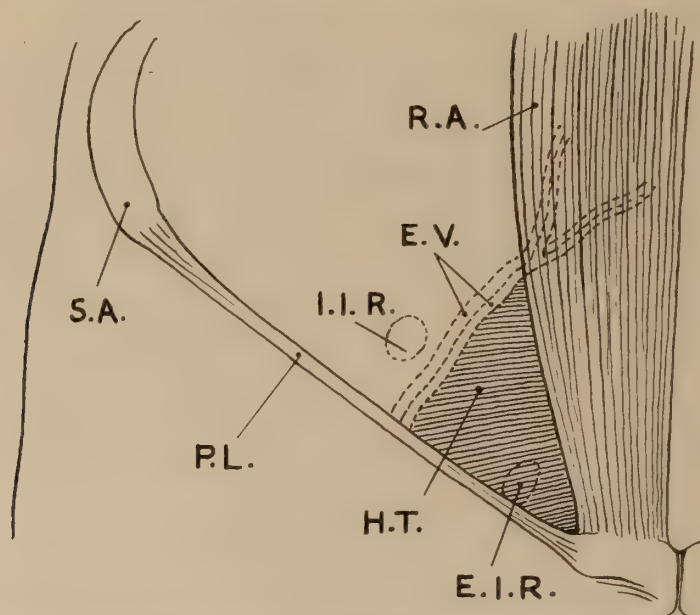


FIG. 1. Schematic representation of Hesselbach's Triangle (shaded area) showing its boundaries and the relative positions of both inguinal rings.

R.A., rectus abdominis muscle; P.L., Poupart's ligament; E.V., deep epigastric vessels; I.I.R., internal inguinal ring; E.I.R., external inguinal ring; H.T., Hesselbach's Triangle; S.A., superior anterior iliac spine.

the necessary requirements for the establishment of this type of hernia, and from the additional fact that they are not infrequently seen in young men who have never worked hard, who are well-nourished, and who have good abdominal musculature. It is apparent that other factors must be taken into account in evaluating the causes for direct inguinal hernia and in explaining its rarity in the female.

Anatomically, the site of occurrence of a direct inguinal hernia is in Hesselbach's triangle, immediately behind the external inguinal ring, where the abdominal wall lacks the strong muscular and fascial support it has elsewhere (3) (fig. 1). Because of its lack of support this area is

known as the "undefended space." It is bounded medially by the edge of the rectus muscle, laterally by the epigastric vessels as they course upward from the external iliac vessels, and inferiorly by Poupart's ligament. The entire thickness of the abdominal wall in this area is made up of the skin, subcutaneous tissue, transversalis fascia and peritoneum. The support rendered elsewhere by the internal oblique and transverse abdominal muscles is lacking here, and the external oblique aponeurosis is defective as well because of the separation of its fibers to form the external inguinal ring.

Several theories have been advanced in an attempt to shed some light on the causation of direct inguinal hernia and to explain the difference in frequency of its occurrence in the two sexes.

1. Cloquet suggested that the transversalis fascia in Hesselbach's triangle was weakened in antenatal life by the passage through it of properitoneal fat which accompanied the penetrating blood vessels (4). This, however, would not explain the rarity of direct hernias in women for there is no evidence that the number of blood vessels or the quantity of properitoneal fat in women is any less than in men. The reverse would seem more likely.

2. Erdman (2) states that an important factor in determining the sex difference may be the wider external inguinal rings found in men. He states that these rings were found pathologically widened in 2.2 per cent of the more than two million men drafted during the World War. Women, he maintains, generally have small external rings. The importance of this factor is apparent when we realize that the larger the size of the external ring the greater will be the area in Hesselbach's triangle left uncovered and unprotected by the external oblique aponeurosis.

3. The cremaster muscle in men may, by exerting traction, weaken the lower fibers of the internal oblique muscle, from which it springs, and concomitantly lessen the support which that muscle renders in buttressing Hesselbach's triangle.

4. Another important etiological factor, suggested by Fallis (5), may be the relatively narrower rectus muscle belly found in subjects with direct hernia as compared with normal controls. The point is made here that since the rectus margin forms the medial boundary of the "undefended space," the narrower the muscle belly the greater will be the area of this space.

Let us now examine briefly the various structures which are encountered in the vicinity of a direct inguinal hernia to see whether we can define the role each may play in its etiology as well as in determining its apparent sex-linkage.

Transversalis fascia. This is a fibroaponeurotic structure which lies immediately external to the parietal peritoneum and forms the first line of

defense against the formation of a direct inguinal hernia. It is mechanically weakest in the midportion of Hesselbach's triangle, where direct hernia normally occurs (2), but its intrinsic structure fails to reveal any differences in the two sexes.

It is pertinent at this time to mention a type of hernia which occurs in Hesselbach's triangle through a sharply circumscribed weakness or defect in the transversalis fascia, and which we may best term a "pseudo-direct" inguinal hernia, or a diverticulum through the transversalis fascia (3). Although this hernia emerges medially to the epigastric vessels and is therefore a direct hernia by definition, its anatomical features differentiate it from the ordinary direct hernia as we are now considering it. In the former, "pseudo," hernia the fascial margins are sharp and firm and the transversalis fascia is everywhere else strong and intact, whereas in the ordinary direct hernia the entire transversalis fascia in that vicinity is diffusely weakened so that no distinct fascial margins are apparent. Because of this the "diverticular" hernia frequently tends to strangulate, a circumstance which practically never occurs with the classical type of direct hernia.

Conjoined tendon. This is the name applied to the fused medial ends of the transversus abdominis and internal oblique muscles but, despite its name, this structure is not always tendinous. The two muscles which give rise to this tendon take origin from the lateral half of Poupart's ligament, just above the region of the internal inguinal ring, and arch medially to insert, as a tendinous structure, behind the external inguinal ring into the pubic crest and ilio-pectineal line anteriorly to the rectus sheath (6). Ideally, therefore, the conjoined tendon should act as a buttress against the "undefended" portion of the abdominal wall and prevent the formation of a direct hernia. In addition the contraction of the combined internal oblique and transversus abdominis muscles should serve to approximate their lower edge to Poupart's ligament, thus serving the purpose of a sphincter and closing any potential weak spot in that area (3). This is the case in rodents and other animals with retractable testes in which the sphincter mechanism is very active (11).

Actually, however, the conjoined tendon is not always the supporting structure it should be. Ochsner (7) states that in certain individuals, especially those with direct hernia, it fails to cover completely the posterior wall of the inguinal canal; as a result, no supporting layer is found in the angle between Poupart's ligament and the rectus abdominis muscle. In others the conjoined tendon is poorly developed and is represented merely by a thinned-out aponeurotic sheet of tissue (3). In all such individuals, obviously, the tendency to hernia is greater than in those in whom a strong tendinous support exists. Finally there are many individuals in whom the tendinous insertion is entirely absent; this condition is stated by Bloodgood to be present in approximately 5 per cent of the population (8). In this condition the muscles have normal origin from Poupart's ligament,

but instead of arching medially to insert into the pubic bone, they continue as muscular structures to insert at varying distances above the pubis into the lateral margin of the rectus sheath. Fallis (5) noted that this condition obtained particularly in people with direct hernias.

Polya (4) made many measurements in people with direct hernias, as well as in normal controls, and found that whereas in the control group the distance upward from the pubic tubercle to the insertion of the conjoined tendon into the rectus sheath practically never exceeded 3 cm., in people with direct hernias this distance varied from a minimum of 3 cm. up to 7 cm. Andrews and Bissell (3) made similar measurements and verified this observation, and Partipilo (8) pursued this a step further in stating that direct hernias may be due primarily to this high insertion of

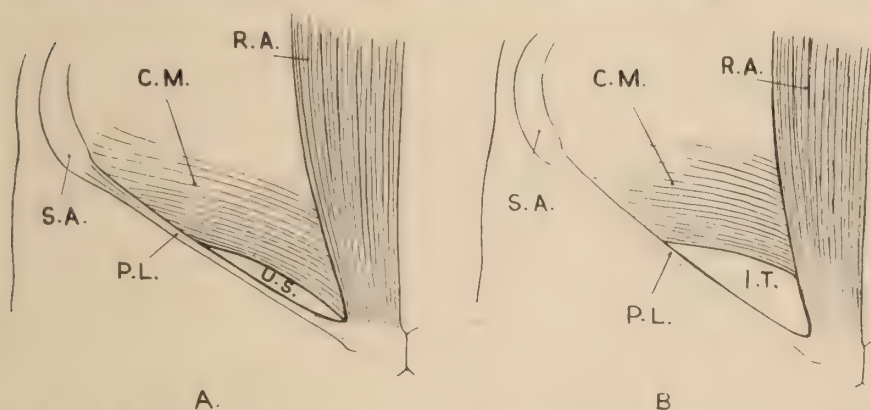


FIG. 2. Sketch showing how the high insertion of the combined internal oblique and transversus abdominis muscles into the rectus sheath creates a large, undefended, "inguinal triangle," as compared with a relatively normal case.

A shows normal insertion of conjoined tendon. B shows high insertion into rectus sheath.

R.A., rectus abdominis muscle; C.M., combined internal oblique and transversus abdominis muscles; P.L., Poupart's ligament; U.S., undefended space; I.T., inguinal triangle; S.A., superior anterior iliac spine.

the conjoined tendon into the rectus sheath. Erdman (2) maintains that in 50 per cent of all people with direct hernias the conjoined tendons are either defective or insert high in the lateral margin of the rectus sheath. In fact, in many cases of direct hernia, Erdman states that a conjoined tendon as such cannot be recognized at all, and the hernial sac presents itself below the edge of the combined muscle bellies.

The insertion of the combined muscles high into the rectus sheath creates an "inguinal triangle" which is bounded superiorly by the fused muscle margins, inferiorly by Poupart's ligament and medially by the margin of the rectus sheath (fig. 2). This inguinal triangle, according to Andrews and Bissell (3), is more important than Hesselbach's triangle, for it is specifically this area which represents the actual extent of weakness of the anterior abdominal wall and which limits the size of a direct inguinal hernia.

It is a wide unsupported area where only the peritoneum and transversalis fascia separate the skin from the intra-abdominal contents.

It is thus apparent that the conjoined tendon is regarded by many observers as an important factor in the protection of the lower abdominal wall since its absence or structural deficiency is evident, in a large percentage of cases of direct inguinal hernia.

Poupart's ligament and the bony pelvis. In lower animals, in which direct hernias are extremely rare, Poupart's ligament usually runs much more nearly parallel to the lateral margin of the rectus muscle than it does in man with the result that the space between the two is very narrow (3). In man, because of the divergent course of these two structures, the aperture between them is wider, resulting in greater opportunity for hernial protrusion.

The interesting observation has been made by Harris and White (9) that the type of hernia present, whether direct or indirect, can be correlated with the length of the inguinal ligament. Briefly, Harris and White state that people with indirect inguinal hernias invariably have inguinal ligaments shorter than 15 cm., whereas people with direct hernias practically always have ligaments which are longer than 15 cm. This distance is measured from the pubic tubercle to the inner side of the anterior superior iliac spine. People who have mixed hernias, of the direct-indirect, or "saddle" variety, have inguinal ligaments which measure close to 15 cm. with but slight variation one way or the other. Using these data Harris and White maintain that in a given individual with inguinal hernia, the longer that person's inguinal ligament the greater is the probability that his hernia is of the direct type.

This isolated observation would mean little were it not for the additional fact that the longer the inguinal ligament the sharper is the angle which it makes with the vertical (9). Thus, the longer inguinal ligaments, such as are associated with direct hernia, are found in the deeper pelvis while the shorter inguinal ligaments are found in the shallower, wider pelvis. Since, however, the typical female pelvis is shallow and wide (10) while the typical male pelvis is steep and narrow it would seem to fit in well with the observations of Harris and White that direct hernias, which are rare in people with wide pelvises, are rare in women, and, conversely, occur predominantly in people with the narrower, male-type pelvises, as in men.

Harris and White also point out that in the deeper pelvis the pelvic floor is relatively more inclined toward the midline, and hence toward the apex of the angle formed by the rectus muscle and the inguinal ligament. It is in this region that the abdominal wall, being at the bottom of an inclined plane and covering the most dependent portion of the abdominal cavity, bears the brunt of intra-abdominal pressure. We have already mentioned, however, that in this area there also exists a relative weakness of the abdominal wall, the so-called "undefended space." Therefore, the combination here of the heightened effect of intra-abdominal pressure

caused by the steep pelvic inclination together with the relative weakness of the abdominal wall at this point certainly seem to predispose to the formation of direct inguinal hernia. In people with shorter inguinal ligaments and with flatter, shallower, pelves, as in the typical female or "gynecoid" pelvis (10), the pelvic floor is only slightly inclined toward the midline, and therefore, the intra-abdominal pressure is more evenly distributed against the anterior abdominal wall, with less tendency to hernia formation.

There is one additional feature which is not mentioned in the literature but which we suggest as being of possible importance in the etiology of direct hernia and in its sex-linkage. By reference to figure 3 it becomes apparent that in the steep, male-type pelvis, the combined internal oblique

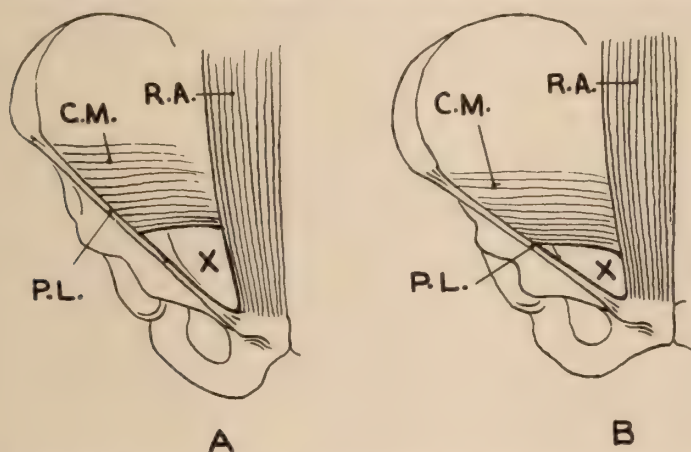


FIG. 3. Diagram showing how variations in pelvic type influence the size of the inguinal triangle (X).

A: Male-type pelvis, with steep angle between Poupart's ligament and rectus muscle, showing high insertion of combined muscles into the lateral margin of the rectus sheath. Note the large, narrow inguinal triangle.

B: Female-type pelvis, showing more obtuse angle between Poupart's ligament and the rectus muscle, with the concomitantly lower insertion of the combined muscles into the rectus sheath. Note the smaller inguinal triangle.

Other symbols are as in previous figures.

and transversus abdominis muscles originate from Poupart's ligament at a relatively greater distance from the pubic tubercle than in the flatter, female-type pelvis. Since these muscle fibers run transversely they would therefore tend to insert into the margin of the rectus sheath at a relatively greater height above the pubis in those with steeper pelves than in the others. Thus, in people with deeply inclined pelves, not only does the undefended space bear the brunt of the intra-abdominal pressure because of its low position at the bottom of an incline, but the conjoined tendon in these cases inserts into the rectus sheath at a relatively high level and thus fails to lend its support to the abdominal wall in that region. Both these factors combine to favor the formation of a hernia through the undefended space.

We may, therefore, reasonably conclude that the shape of the pelvis, particularly in regard to its steepness or flatness, is of paramount importance in determining susceptibility or immunity to the formation of a direct inguinal hernia. Since pelvis type is intimately related to the sex of the individual, flatter pelvis being more common in women and steeper pelvis more frequent in men, this may help explain the predominant occurrence of direct hernia in men and its relative rarity in women.

SUMMARY

Because of the rarity of direct inguinal hernia in the female a study was made to try to determine what factors were at play in favoring the occurrence of this type of hernia in the male.

A brief anatomical description of the area involved is given together with a short discussion of the roles played by the various pertinent anatomical structures.

CONCLUSIONS

We believe that the most important factor in determining the susceptibility or immunity of an individual to the formation of a direct inguinal hernia is the type of pelvis which that individual possesses. The presence of a narrow, steep pelvis, the so-called masculine or android type (10), favors the formation of direct hernia because it projects the force of intra-abdominal pressure against the "undefended space" in the lowest part of the anterior abdominal wall. The flatter, female-type, pelvis favors a more equitable distribution of intra-abdominal pressure against the lowest portion of the anterior abdominal wall, and so prevents the brunt of pressure from falling on Hesselbach's triangle.

The conjoined tendon in the steeper pelvis inserts high in the lateral margin of the rectus sheath and so fails to lend its support to the "undefended space," while in the shallower, flatter pelvis the conjoined tendon inserts relatively lower, usually into the pubic tubercle, and thus helps to protect this area.

The fact that oblique or narrow pelvis are characteristic of the male while the flatter pelvis occur generally in the female explains why direct inguinal hernias are practically confined to the male sex.

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HERNIA IN THE LINEA SEMILUNARIS

IRVING A. SAROT, M.D.

[From the Surgical Service of Dr. Harold Neuho]f]

Spontaneous lateral ventral hernia occurs infrequently. When it occurs, however, the most frequent variety is hernia in the linea semilunaris, first described by La Chausse in 1721. Barthelemy (1), in 1919 could collect from the literature only twenty-three cases including one of his own but since then much work has been done on this subject, and at present there are ninety-two reported cases. Because these cases apparently constitute a definite clinical entity, another case is reported which occurred recently.

CASE REPORT

History (Adm. 377061). The patient was a 58 year old man, a private patient of Dr. Harold Neuho]f. For twenty years he had had occasional attacks of dull, right lower quadrant pain, which was vague and not very severe, except on one occasion about five years before admission, at which time the diagnosis of acute appendicitis had been made. The attacks of pain had usually subsided rapidly and spontaneously. On admission he complained of constant, dull, crampy pain for twenty hours, well localized to the right lower quadrant. He had experienced no other symptoms, and was afebrile.

Examination. The abdominal wall was entirely relaxed, and there was moderate tenderness in the right lower quadrant, maximal at McBurney's point. An indefinite, slightly tender mass was felt in the region of McBurney's point on light palpation; but on deep pressure the abdominal muscles became spastic and the mass could not be felt. Rectal examination was negative. The history, the mass without fever, and the presence of a mass so soon after the onset of symptoms could not be fitted into the clinical picture of appendicitis. Nevertheless, it was decided to perform a laparotomy.

Operation. When the patient was under anesthesia, a rounded mass, three by two centimeters, was felt in the abdominal wall at McBurney's point. A McBurney incision was made and when the external oblique aponeurosis was split a tense sac, about six by four centimeters, was exposed. The contents were seen to be moving freely within the thin peritoneal membrane. The sac had a narrow neck projecting through a defect of the tendinous junction between the internal oblique and the rectus sheath. When the peritoneal sac was split upward and medially, it was seen to contain two small elongated pads of fat, each on a long thin fibrous pedicle, apparently arising from the omentum. These were amputated, and the appendix, free from any evidence of infection was delivered through the hernial sac and removed. The sac was ligated and amputated, and the fascial defect closed by overlapping the edges. Postoperative recovery was without significant features.

DISCUSSION

Hernia in the linea semilunaris, medial to the deep epigastric artery, is usually classed with direct inguinal hernia. Hernia lateral to the deep

epigastric artery, the one with which we are concerned, rarely occurs above the umbilicus and most frequently appears in the zone near the level of the semilunar fold of Douglas. The hernia may be situated at the weak point of the semilunar fold of Douglas where the posterior rectus sheath is deficient; but the sac may protrude through small actual defects of the linea semilunaris. Koljubakin, reporting eight cases and studies on thirty cadavers of various ages, found that the protrusions usually occurred where the blood vessels pierced the aponeurosis of the transverse abdominal muscles. This is an exceedingly interesting substantiation of the point of view held by Moschcowitz that hernia regularly occurs at the site of perforation of vessels. Costa collected from the literature the research of several workers, including Koljubakin (3), on sixty-five cadavers and found that 45 per cent presented uni- or bilateral lacunae in the linea spigelia (linea semilunaris) from 3 mm. to 37 mm. in diameter, always associated with some nerve or blood vessel piercing the fascia. He felt that these lacunae offered zones of lessened resistance to strain. Koljubakin and others stressed the fact that properitoneal lipomata were frequently found in this region and were even more frequently found in front of the protruding hernial sac. These workers felt that sudden severe strain might cause a propulsion of such lipomata through the fascial defects existing in the course of perforating blood vessels and nerves.

In rare instances a hernia in the linea semilunaris may have more than one opening through the aponeurosis. There is always a hernial sac, even to the size of a small orange in one case. Very frequently a properitoneal lipoma has been found in association with the sac and indeed, in many cases a lipoma has constituted the greater part of the mass. The sac has contained omentum or small intestine in most instances. A case in which the sac contained a Meckel's diverticulum has been reported by Massabau (7). Because of the narrowness of the neck of the sac and its distensibility with increased intra-abdominal pressure, strangulation of the contents is a frequent complication. These hernias are usually interstitial, situated beneath the external oblique aponeurosis and in front of the transversalis fascia. In rare instances a portion of the hernia may even be subcutaneous.

Because of the small size of these hernias and because of their deep interstitial location diagnosis is difficult. From a study of the reported cases the conclusion can be drawn that the diagnosis usually was made when symptoms appeared due to incarceration and possibly strangulation of contained intestine or omentum, and even then only when a mass was visible or palpable in the region of the linea semilunaris. Frequently, however, there was only a localized point of tenderness and the interstitial mass was not palpable. In many cases the picture resembled that of an acute intra-peritoneal infection or of an intestinal obstruction. In other instances the diagnosis was made only on exploratory laparotomy. It is of note that when there was a localized tender area a cough impulse could sometimes be felt at that site.

The reported case conforms with the above abstract of the literature. It appears to have been the first noted in this hospital. At first regarded as a unique curiosity, after perusal of the literature, the fact was appreciated that the lesion is not rare; that it can be diagnosed at least in some instances, if its possible existence is borne in mind, and that its recognition is a matter of some clinical importance.

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AN UNUSUAL TYPE OF DIRECT INGUINAL HERNIA

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[From the Surgical Service of Dr. Harold Neuhoﬀ]

The purpose of this communication is to describe an unusual type of direct hernia and to indicate wherein it differs from the usual varieties. A. V. Moschcowitz (1) stated: "Every hernia which makes its escape from the abdomen on the mesial side of the deep epigastric artery is called a direct inguinal hernia." He further pointed out that a hernia of Hesselbach's triangle is usually small and only rarely descends into the scrotum. The peritoneal sac is considerably smaller than the size of the hernial mass would lead one to believe. The reason is that an appreciable part of the protrusion consists of properitoneal fat, more abundant in this region than in the zone of indirect inguinal hernias. Davis (2) found that a direct inguinal hernia almost always enters the middle inguinal fossa between the hypogastric and epigastric arteries, that is, lateral to the hypogastric fold. Herniations mesial to the obliterated hypogastric artery are very rare.

Deaver (3) and Watson (4) also have emphasized that hernias of the direct type present a bulge of the peritoneum rather than a true sac, as in the indirect type. Finochietto (5, 6), who has contributed much to the pathology and pathogenesis of direct hernia, finds that in all cases there is atrophy of the conjoined tendon, as described by Hessert (7), and that the cremaster muscle is absent in most cases. He has found that the form of the sac varies according to its size from the simple dome-shaped bulge to the true sac, and that the base of the tumor is always very broad. He classifies direct hernias into three varieties:

1. Saccular (73 per cent), in which the tumor is hemispherical and the sac consists of transversalis fascia (primarily at the base), properitoneal fat (likewise most prominent at the base) and peritoneum.

2. Lipomatous (20 per cent), in which a clear yellow fatty lobule, completely encapsulated, presents a strangulation which corresponds to the external ring. The sac is always small and thin.

3. Splanchnic (6 per cent), in which a viscus (for example, the bladder) takes part in the formation of the tumor. This type is frequently large and difficult to reduce.

The case described here presents several unusual features. The hernial orifice was located in the inner and lowermost corner of Hesselbach's triangle, mesial to the hypogastric artery. As already noted, this is a very

rare location. The opening was a narrow defect in the transversalis fascia with sharply defined margins which just admitted the index finger. This opening was quite disproportionate to the size of the sac, which was elongated and about four inches in length. The sac was pear-shaped with a constricted neck, as contrasted with the usual dome-shaped bulge with a broad base. Furthermore, the sac wall was uniformly well developed and contained throughout a substantial peritoneal layer and a well distributed thin pad of properitoneal fat. This direct hernia obviously differs in most respects from the well recognized types of hernia of Hesselbach's triangle.

A review of the literature revealed only one comparable case. Banks (8) reported a case in which the hernia consisted of a mass of extra peritoneal fat protruding through an opening in the abdominal wall the size of a "cedar-wood pencil." The defect was lateral to the rectus sheath and one-half inch above the pubis. There was a process of peritoneum in the fat, but no abdominal contents. The similarity to the present case lies in the location of the hernial orifice and its restricted nature, but it differs in that it had a very small peritoneal sac with a large mass of extra-peritoneal fat.

CASE REPORT

History (Adm. 375785). L. G., a Russian-Jewish furrier, 45 years of age, was admitted to The Mount Sinai Hospital on January 17, 1935 complaining of a bulge in the left groin of sixteen years' duration. While raising water from a well he felt something "break" in his left groin. Shortly afterward he noticed a swelling in this region, but experienced no pain. He began wearing a truss almost immediately, but despite this precaution the bulge progressively increased in size. It was always readily reducible. During the year preceding admission he had frequent cramp-like pains in the left inguinal region. The past history was otherwise not remarkable.

Examination. Except for the inguinal regions, the examination was negative. The left external ring was dilated and admitted the tip of the finger. It transmitted an impulse on coughing. There was a plum-sized bulge in the inguinal region on straining. This seemed to be direct in nature and did not descend into the scrotum. There was a smaller similar bulge in the right groin.

Operation. A five inch left inguinal incision was made through the skin. The aponeurosis of the external oblique was divided in the usual manner, and the cord and its structures were identified. A fairly large hernial bulge, approximately the size of a lime, was exposed posterior to the spermatic cord. The sac was freed from the cord structures. It was then opened and dissected down to its neck. The deep epigastric artery was seen to run definitely lateral to the neck of the sac, and was not displaced by the herniation. The sac itself was fully four inches long and was well developed, containing all of the peritoneal layers including fat. The content of the sac was a non-adherent omental wedge. The sac protruded through a well defined defect in the transversalis fascia. This was approximately one inch in length and located in the inner and lowermost corner of Hesselbach's triangle. Traction upon the sac brought a portion of the bladder into the hernia; but bladder was not truly a hernial content. The excess sac was resected and the peritoneal opening closed. The defect in the transversalis fascia was approximated over the peritoneal stump. The usual Bassini repair was done with transplantation of the cord.

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HERNIATION OF THE URINARY BLADDER

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It is not uncommon during a routine herniorrhaphy to encounter a herniation of the urinary bladder through the inguinal or femoral rings. Various observers estimate that from one to three per cent of all hernias contain a bladder component (1, 2).

It is unusual, however, for the diagnosis to be made pre-operatively. In part, this is due to lack of outstanding urinary symptoms in the majority of patients. Robnett (2) states that the correct pre-operative diagnosis is made in less than ten per cent of all cases. Vastola (3) reviewed twelve cases of strangulated femoral cystocele and found that in not a single instance was the bladder herniation suspected pre-operatively.

The importance of a correct diagnosis is appreciated when it is realized that a bladder injury is not always recognized during the hernioplastic procedure. Failure to properly repair the injured bladder may lead to very serious complications. Hunnicutt (1) reported a mortality as high as thirty to forty per cent and a high incidence of postoperative urinary fistulae. On the other hand, when proper and complete repair of the injured viscus is effected serious harm does not usually result.

There are but few instances in the literature in which the diagnosis was made pre-operatively by the relatively simple procedure of retrograde cystography. Levy (4) reports a case; Bierhoff and Unger (5) present another and refer to one described by Makkas (6). Because of the not infrequent occurrence of this condition, Hinman (7) suggests the employment of routine cystography for all inguinal hernias in men past the age of fifty years.

CASE REPORTS

Case 1. History (Adm. 439986). N. K., a 50 year old man, was admitted to The Mount Sinai Hospital on May 6, 1939 for the repair of a right complete indirect inguinal hernia which had been present for three years. For five months the patient had noted that the hernia was considerably larger when he awakened in the morning. After voiding, the right scrotal mass was partially reduced in size; further voiding could be forced by pressure on the hernial mass. More recently, reduction in size was not as pronounced after urination. Eleven days before admission there was an acute episode of complete urinary retention. There was never any dysuria until recently when diurnal frequency with occasional mild urgency was noted. There had never been any hematuria, pain or burning sensations.

Examination. A large, incompletely reducible, right indirect inguinal hernia was present which descended into the scrotum. The right testicle was felt in the lower portion of the scrotum and the mass above it was flat to percussion; it was not translucent. Bladder dullness extended to the umbilicus. The prostate was not thought to be enlarged as determined by rectal palpation.

The bladder was catheterized and the scrotal mass became smaller. Culture showed the presence of *B. proteus* and *staphylococcus albus*. Urinalysis revealed a two plus albumin and one to two red blood cells per high power field with an occasional clump of white blood cells. No residual urine was obtained from the bladder after voiding.

Course. On the day after admission, the patient passed a marble-sized calculus *per urethram* and several hours later had a chill with a temperature rise to 104.6°F. On the following day the temperature became normal and remained so throughout the hospital stay.

A retrograde cystogram (fig. 1) was done several days after admission and showed a large bladder hernia descending into the right scrotum. The pelvic portion of the



FIG. 1. Case 1. Black arrows outline herniated portion of urinary bladder. White arrow points to calculi in the bladder hernia.

bladder was pulled towards the right. Within the opacified herniated portion of the bladder were seen two circular filling defects, each about 1 cm. in diameter, interpreted as vesical calculi. The prostate indented the base of the bladder to a slight degree.

Operation was not performed at this time and the patient was discharged.

Two months later he returned to the Out-Patient Department and reported the passage of a small calculus two weeks previously.

On January 20, 1940, the patient complained of a sensation of "urine in the scrotum" when voiding. The hernia mass did not decrease in size after urination as it had previously. Examination showed the hernia to be of grapefruit size and irreducible. The mass above the right testicle was described by the examiner as being "continuous with the abdominal contents."

Second admission. The patient was re-admitted to the hospital for operation. Cystoscopy showed no residual urine; the communication between the pelvic and hernial portions of the bladder was not visualized. Numerous small uric acid calculi were seen. Moderate lateral and middle lobe enlargement of the prostate was described. Pre-operatively, an indwelling catheter was inserted and after introducing fluid into the bladder, the hernial sac was noted to enlarge. A second retrograde cystogram showed no change in the radiographic appearance.

Operation (Dr. G. D. Oppenheimer). The cord and cremasteric muscle and fascia were dissected off the hernia and at the upper lateral portion of the hernia a peritoneal sac was opened. The peritoneal component was about one-fourth the total hernial mass, the remainder being bladder. There was no evidence that the bladder mass was a diverticulum. The bladder was pushed into the external peritoneal suprapubic area without much difficulty and a modified Andrews-Bassini hernioplasty was performed with subcutaneous transplantation of the cord.

A cystogram taken thirteen days postoperatively showed the bladder to be in normal position.

Case 2. History (Adm. 454205). N. B., a 62 year old man, was admitted to The Mount Sinai Hospital on March 25, 1940. He had had a hernioplasty thirty-five years previously for a left inguinal hernia. Three years before admission there was a recurrence of the hernia which descended into the scrotum. At first, reduction could be maintained with a truss, but recently the truss was ineffectual. Descent of the hernia into the scrotum was associated with severe pain in the left groin and frequent irreducibility. At these times there was marked tenderness and enlargement of the scrotal mass. Eight months prior to admission the patient developed urinary symptoms, i.e., frequency, nocturia (8 times), urgency, burning sensation on micturition, delay in initiating urination, lack of force behind the urinary stream, irregularity and cessation of flow with straining. Despite these urinary complaints, the patient was more disturbed by the hernia.

Examination. An irreducible, complete, direct left inguinal hernia was present. It was not translucent. The prostate was enlarged as determined by rectal palpation. A barium enema showed all of the sigmoid intestine to be in the left scrotal hernia (fig. 2); there was narrowing of the bowel at its entrance into and exit from the inguinal ring. These loops remained filled with barium after evacuation. A residual of one ounce of urine was obtained from the bladder after voiding. It was thought that the urinary symptoms might have been due to a sliding hernia of the bladder; however, a retrograde cystogram was not done.

Operation (Dr. H. Neuhof). Laparotomy was performed with the idea of relief of bowel obstruction rather than cure of the hernia. The inguinal ring was exposed from within and incised; the sigmoid was drawn back into the peritoneal cavity and its peritoneum ablated down to the region of the bladder. The bladder did not appear to enter the hernia. Repair of the peritoneal opening was completed.

Postoperative course. The patient was unable to void on the day following operation; by catheterization sixteen ounces of blood-stained urine was obtained. During the following ten days, the patient was unable to void spontaneously. On the tenth postoperative day, the hernia recurred. Because of the persistent urinary retention, cystoscopy was performed and moderate enlargement of all the prostatic lobes was noted. Trabeculation of the bladder was noted and numerous pin-head sized uratic calculi were seen. A retrograde cystogram was now done and the bladder hernia descending into the scrotal mass was demonstrated (fig. 3).

Transurethral resection for relief of urinary obstruction was performed; seven grams of prostatic tissue was removed from the middle and lateral lobes. The postoperative course was satisfactory. After three days, the catheter was withdrawn and the patient was able to void spontaneously with moderate dysuria. No residual

urine was demonstrable. Changes in size of the hernia, following urination, were not recorded. The patient was seen on June 4, 1940 complaining of pain in the suprapubic region with inability to empty the bladder completely; nocturia (12 times);



FIG. 2. Case 2. Upper arrow indicates constriction of the sigmoid where it passes through the inguinal ring. Lower arrows outline herniated sigmoid loops.

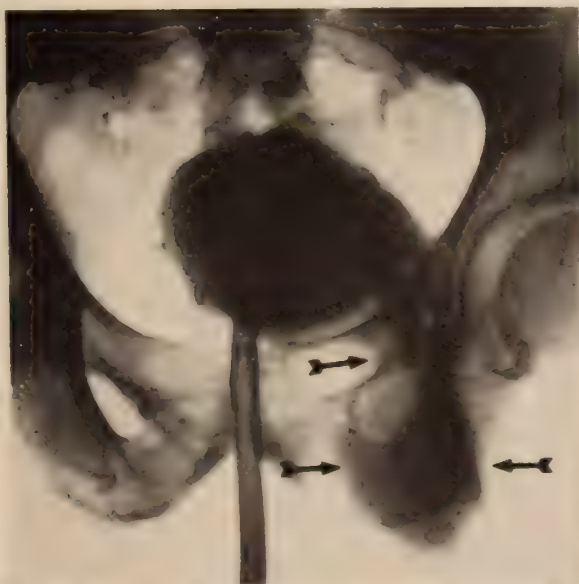


FIG. 3. Case 2. Arrows outline herniated process of urinary bladder.

and thirty minute frequency during the day. The bladder was irrigated; no residual urine was found.

Further surgical procedures are now being considered.

DISCUSSION

Types. Anatomically, there are three major types of true vesical herniation (extroversion and vaginal cystocele are not considered in this classification): 1) Intraperitoneal, in which the bladder process is contained within the hernial sac; 2) Paraperitoneal, in which the herniated process is covered only on one side by peritoneum. This is the most common, and 3) Extraperitoneal, in which there is no peritoneal covering. The prolapsed bladder is neither present in nor enters into the formation of a hernial sac. If a sac is present, the bladder is distinct from and medial to it.

The extremely rare occurrence of the following types has been recorded: 1) Obturator extraperitoneal; 2) Suprapubic, through the linea alba; 3) Ischiorectal. 4) A type is described by Gironcoli (8) which protrudes directly through the belly of the rectus abdominis and has for its ring the rectus fascia and muscle.

All types may be either complete or incomplete; the inguinal varieties may be direct or indirect. Any of the viscera commonly found in hernias may be present in addition to the bladder prolapse.

The bladder process may represent herniation of a vesical diverticulum and the stoma communicating with the pelvic bladder may be narrow or wide.

When the herniation of the bladder descends into the scrotum, the cystographic appearance is typical. However, when the hernia is incomplete, differentiation must be made between actual herniation of a part of the bladder into the inguinal or femoral rings and projection of a large diverticulum towards the pelvic floor. Oblique and lateral films of the opaque-filled bladder process are of aid in making this differentiation.

SUMMARY

1. The urinary bladder is a component in one to three per cent of all hernias.

2. Retrograde cystography is a simple procedure which can be employed preoperatively to exclude the presence of bladder herniation. This procedure might be especially valuable in men past the age of fifty years.

3. Two representative cases of vesical hernia are presented with illustrative cystograms.

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INCARCERATED FEMORAL HERNIA CONTAINING AN ADHERENT APPENDIX

REPORT OF TWO CASES IN MEN

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The occurrence in a man of a femoral hernia containing an appendix is extremely rare. Case 1 to be reported is most unusual because there were no symptoms referable to the hernia and because the appendix was adherent to the femoral sac.

CASE REPORTS

Case 1. History (Adm. 436264). A sixty-four year old man was admitted to the hospital on February 14, 1939 because of a mass in the right groin of several months' duration. The past medical and surgical history was irrelevant. The small firm tumefaction was noted several months before admission. It caused no pain and there were no related gastro-intestinal symptoms. The mass did not vary in size.

The general physical examination was essentially negative. In the right femoral region there was a firm, non-tender, tense, irreducible mass about 4 cm. in each diameter.

Operation for incarcerated femoral hernia was performed under avertin gas-oxygen ether anesthesia. The right femoral region was exposed through a liberal incision parallel to and below Poupart's ligament. A tense thick-walled sac was visualized and isolated. It was opened and fluid was evacuated; the thickened appendix, intimately adherent to the wall of the sac, was the prominent feature of the contents of the sac. The appendix was freed by sharp dissection and drawn out of the wound with part of the cecum. The mesenteriolum was severed after it had been ligated, and the base of the appendix was ablated with the high frequency current. The hernial sac was freed and ablated at the neck, and the hernial space obliterated by uniting the lower edge of Poupart's ligament to the pectineus fascia. The skin was closed without drainage.

The postoperative course was uneventful and the patient was discharged on the eighth postoperative day.

There was another case in The Mount Sinai Hospital records of a man with a femoral hernia containing an appendix. The features of the case can be stated briefly.

Case 2. History (Adm. 377764). This patient was fifty-six years of age and had been operated upon twenty-three years previously for a bilateral inguinal hernia. Ten days before this admission he noticed an irreducible mass in the right groin, associated with pain and vomiting. Examination revealed an incarcerated right femoral hernia. At operation the sac was found to contain the distal third of the appendix which had become hemorrhagic due to strangulation. The entire appendix

could not be delivered readily and only the diseased portion was removed. The hernia was repaired in the customary manner. There was a mild infection of the wound but the postoperative course was otherwise uneventful.

DISCUSSION

In 1906 Wood (1), reviewed 3,054 cases of hernia and reported the presence of the appendix alone or with other viscera in 58 or 0.19 per cent. In 1910 Grey (2) reported 59 cases of hernia of the appendix. He stated that strangulation of the appendix in the hernial sac was more common in femoral hernias, and inflammation of the appendix was more frequent in inguinal hernias. Coley (3) found ten cases in which the appendix alone

TABLE 1

Analysis of cases of femoral hernia at The Mount Sinai Hospital (1928 to 1938)

Total number of cases.....	213
Sex	
Women.....	167
Men.....	46
Contents of hernial sac (men)	
Omentum.....	11
Small intestine.....	9
Appendix epiploic.....	1
Appendix.....	1
Empty.....	25
Not mentioned.....	2
Side (men)	
Right.....	28
Left.....	15
Bilateral.....	3

TABLE 2

Femoral hernia of the appendix in men as reported in the literature

Watson.....	4
McClure and Fallis.....	1
Doolin (quoted by McClure).....	1

was present in the hernial sac in a series of 2,200 hernia operations. In 1923 Watson (4) collected 512 cases of hernia of the appendix. Of these 269 were inguinal, 217 femoral, and 2 obturator hernias. In 181 cases in which the sex is stated, 177 were women, and 4 were men. Shawan and Altman (7) described three cases in women. In 1939 McClure and Fallis (8) reported two cases in men (one of their own and one from the literature).

In a review by the author of 213 cases of femoral hernia operated upon at The Mount Sinai Hospital for a period of eleven years (1928 to 1938 inclusive), 46 were men. In one of these the sac contained an appendix (case 2 in this report). Thus, with the two cases herein reported, a total number of eight femoral hernias of the appendix in the male are on record (table 2). Watson (5) states that femoral hernias comprise 40 per cent of

all the cases of hernia in which the sac contains the appendix; about 2 per cent of these are in men. Adhesions of the appendix are common in this variety of hernia, the appendix being adherent in about 95 per cent of the cases. In both of the cases reported the appendix was adherent to the sac.

SUMMARY

Femoral hernia of the appendix in men is discussed and two cases reported. A review of the literature revealed six similar cases. The unusual combination in a man of a femoral hernia containing an adherent appendix warrants the reporting of these two cases.

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REDUCTION EN MASSE OF A STRANGULATED HERNIA. OPERATIVE CURE

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The purpose of this paper is to present a case of reduction en masse of a strangulated inguinal hernia and to discuss its mechanism and management.

CASE REPORT

History (Adm. 441713). A 38 year old, unmarried pharmacist had a left inguinal hernia for ten years which had gradually grown larger, but never so large as to descend into the scrotum. It had always been reducible and had caused him no discomfort except for an occasional dragging sensation in the region of the hernia. There were never any symptoms suggesting incarceration. The patient had worn a truss for several years.

Two and a half days prior to admission, while retiring, the patient was seized with generalized cramp-like abdominal pain and a feeling of distention. The pain became increasingly severe and an hour later when he got out of bed and attempted to have a bowel movement, he vomited some non-odorous dark brown material. After this episode of vomiting, he noticed that the hernia appeared and he was unable to reduce it. He stated that he did not use much force in attempting reduction. The pain and vomiting persisted throughout the night. The next morning he called a physician who attempted reduction of the hernia unsuccessfully and then administered a hypodermic. His condition remained unchanged and twelve hours later another physician was able to reduce the mass upon light taxis but without a gurgle. Following reduction, the truss was replaced over the inguinal region. The vomiting and cramps continued, however, and the next day he was brought to a hospital where he received parenteral fluids. Twelve hours later he was transferred to The Mount Sinai Hospital. During the course of his present illness, the patient had neither a bowel movement nor passed any flatus.

Examination. The patient was a thin well developed man appearing acutely ill. His temperature was 99°F., his pulse rate 88 per minute and respirations 20. The abdomen was moderately distended and diffusely tender particularly in the left lower quadrant where a sense of resistance could be felt above and mesial to the internal ring. No hernial mass could be felt in the inguinal canal on the left side. The external ring was considerably dilated and a feeble impulse on cough could be elicited.

Course. In view of the history of an incarcerated hernia reduced upon light taxis without a gurgle, together with the signs and symptoms of persisting intestinal obstruction, and the presence of a mass in the left lower quadrant medial to and above the inguinal canal, the assumption of a reduction *en bloc* was warranted. A Levin tube was passed yielding upper intestinal contents and an intravenous infusion of 5 per cent glucose in normal saline was begun prior to operation.

Operation. Under spinal anesthesia, a left lower rectus muscle-splitting incision was made. As the peritoneal cavity was entered, a large amount of clear amber colored fluid escaped and there presented both dilated and collapsed small intestine.

On exploration of the abdominal cavity, a mass was felt in the left lower quadrant and the incision had to be extended downward. A tense bluish sac could then be visualized above and medial to Poupart's ligament. The orifice of the sac was a narrow fibrous ring protruding into the peritoneal cavity. Mesial to it was another bulge apparently due to the rest of the sac outside the abdominal cavity. Into the sac there entered greatly dilated small intestine, and out of it there emerged collapsed intestine. The orifice was gently dilated with a ring clamp and the strangulated bowel as well as some bloody fluid was released. About one and a half inches of bowel appeared strangulated. This loop showed a reddish, mottled circular area about one inch in diameter on the antimesenteric border. The mesenteric border was slightly indurated. The involved loop was covered with a warm packing. The sac which had already partially invaginated into the peritoneal cavity, could be completely pulled out through the ring and was then found to be about two and one-half inches in length. The sac was excised proximal to the ring, revealing some blood vessels and a layer of tissue which may have been transversalis fascia. The peritoneum was sutured without tension. Thus, there was achieved the removal of the sac which had been reduced *en bloc* into the peritoneal cavity. The loop of intestine was now more carefully examined and then returned to the abdominal cavity after satisfactory evidence of its viability was obtained. The abdominal wall was closed in layers without drainage. No hernioplasty was performed.

Postoperative course. On the fifth postoperative day the temperature became normal and the Levin tube drainage and administration of parenteral fluids were discontinued. On the sixth postoperative day the patient had a spontaneous bowel movement. On the fourteenth day he was discharged with the wound healed by primary union. He was examined four months later, and again one year later, during which time he had remained well. The scar in the left inguinal region was firm and there was no evidence of herniation.

DISCUSSION

There has been very little attempt in the literature to correlate various concepts concerning this topic with the individual cases presented. It is fortunate that this case lends itself to an empiric elucidation of some of these concepts. In discussing the etiology of "reduction en bloc", Pearse (1) said that if an inguino-properitoneal hernia is present, there can occur spontaneous shifting of a strangulated loop from the inguinal to the properitoneal locus of a bilocular sac. Likewise there is no reason to suppose that a shift in the reverse direction cannot occur as well. It can be postulated, therefore, that in this case there was an inguino-properitoneal sac in which the bowel first became incarcerated in the properitoneal position. The history at the onset is typical of incarceration without the appearance of a hernial mass. The hernia appeared only after vomiting and straining. At that time there probably occurred a spontaneous shift from the properitoneal to the inguinal locus. In the original properitoneal locus, the patient could not have been aware of the presence of a hernia since on admission to the hospital, when the hernia had been reduced again to the properitoneal locus, he was not then aware of the presence of a hernia. The "reduction en bloc" effected by the surgeon was therefore merely a shift of the strangulated loop back to the properitoneal position.

It is impossible to state whether this patient had a congenital or acquired bilocular sac. He had no undescended testicle or narrow external ring. He did, however, have a small, repeatedly reducible hernia for a long period of time; and he wore a truss which may have fitted imperfectly and produced the same mechanical effect as a narrow external ring. In addition this sac had a narrow neck. All of these factors provided ample opportunity over a period of years for the development of a properitoneal space if one was not congenitally present.

The physical examination and operative findings are of importance in increasing the evidence for the presence of a bilocular sac in this patient. An indefinite mass could be palpated abdominally, more as a sense of resistance medial to and above Poupart's ligament. Yet at operation, there was a bulging of the anterior parietal peritoneum into the abdominal cavity just mesial to the partially invaginated neck of the sac. If the sac had been present in the space between the internal oblique muscle and the external oblique aponeurosis, the hernia with its contents should have been readily palpable particularly in a thin individual. The sac could possibly have been in the space between the transversalis fascia and the transversus muscle, but upon excising it in a circular manner a layer of tissue with blood vessels appeared resembling transversalis fascia, certainly not muscle. Another significant operative finding suggesting a preformed properitoneal pouch was the discrepancy between the size of the strangulated loop (one and a half inches) and the size of the sac (two and a half inches).

SUMMARY

The evidence indicates that an inguino-properitoneal sac existed in the properitoneal component of which a loop of ileum became incarcerated with ensuing symptoms of intestinal obstruction. During an episode of vomiting the position of the strangulated loop became inguinal, the strangulation at the neck of the sac persisting. Thereafter an apparent reduction was effected by taxis, the strangulated loop being returned to its original properitoneal site. There it remained until released by operation.

The other feature of interest is the cure of the hernia. This was achieved (one year follow-up observation) by an emergency operative procedure which consisted solely of ablation of the sac from within the peritoneal cavity.

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STRANGULATED RICHTER'S HERNIA. OPERATIVE TREATMENT BY LAPAROTOMY

HAROLD NEUHOF, M.D.

Defining Richter's hernia as a sac containing a protrusion of only a portion of the circumference of the intestinal wall, and a strangulated Richter's hernia as one in which only a portion of the protruded circumference of the bowel is caught in a hernial sac, strangulated Richter's hernia can be regarded as a rare lesion. In most of the cases in the literature the lesion whether obstructed or not is situated within a small femoral sac. It is presumably because the hernia is small that its existence has not been recognized before operation in a substantial portion of the reported cases of strangulated Richter's hernia. In addition, the diagnosis is rendered difficult because the obstruction, involving only a portion of the bowel, is incomplete. The operative treatment, when the diagnosis of strangulated Richter's femoral hernia is made, has usually consisted in incision over the femoral sac with release of the obstruction and the management of the involved bowel in accordance with the extent of the damage. The purpose in reporting the following case is to describe the management of both the intestinal obstruction and femoral sac by way of an abdominal and not the conventional femoral approach.

CASE REPORT

History (Adm. 468029). S. S., a woman, 45 years old, was admitted to the Private Pavilion of The Mount Sinai Hospital on January 17, 1941. A left femoral hernia was known to have existed for a considerable length of time. Abdominal cramps, nausea and vomiting began five days before admission, and there was noted a slight increase in the size of the hernia. It was found to be irreducible. The symptoms of an intermittent partial intestinal obstruction persisted throughout these five days.

Examination. On admission, the patient was acutely ill and dehydrated. In the left femoral region there was a small tense tender reddened tumefaction. The abdomen was not greatly distended.

Operation. A low left vertical rectus-splitting incision was made. Distended loops of intestine were packed away. A partially collapsed loop of small intestine was noted. It was traced to its exit from the region of the internal ring of the femoral canal. With the peritoneal cavity completely packed off and the patient in the Trendelenburg position, the tight ring was visualized. Its margins were caught with forceps and the ring was incised. The loop of intestine was thereby suddenly released and could be brought into the abdomen without traction. It was packed off for later inspection and the contents of the sac, consisting of grumous bloody fluid, were evacuated by suction. The loop of intestine was now examined. The area which was strangulated was a diverticulum-like projection of the small bowel opposite the mesentery. It was elevated about a half inch above the level of the adjacent

bowel. Its serosal surface was acutely inflamed and was partly covered by a small patch of exudate. There was a constriction at the base of the diverticulum-like projection. In the line of the persisting constriction there was cicatricial tissue suggesting that the projection had existed for a considerable period of time. Even at the end of operation at the time of closure of the peritoneal cavity, the projection remained. In the absence of any evidence of necrosis, and with some return towards normal appearance of the involved portion of bowel, no further surgical treatment appeared indicated. Accordingly, the loop was surrounded by warm pads and the region of the femoral sac was exposed. By the successive application of clamps, the sac was drawn up into the peritoneal cavity, ablated, and the defect closed by sutures which drew together the parietal peritoneum at the edge of the internal ring. The abdominal wall was closed in layers.

Postoperative course. There was a thoracic postoperative complication consisting of pain in the right chest, cough, and slight hemoptysis. Fever set in later. There were physical signs of fluid in the chest and aspiration revealed old tarry blood in the pleural cavity. Convalescence was prolonged because of this complication. The patient was discharged from the hospital three and a half weeks after operation at which time there was some complaint of abdominal cramps.

Abdominal cramps persisted from time to time for a period of six weeks after discharge from the hospital. They have now subsided completely and the patient remains symptom-free.

Roentgenographic studies made three months after operation revealed no abnormalities in the small bowel.

COMMENT

Since there always is a mortality to be considered in the operative treatment of strangulated hernia, the management of any case in which a loop of bowel is compromised should be directed primarily, if not solely, towards the saving of life. The operative release of strangulated bowel through the customary inguinal or femoral approach may be fraught with difficulty, and as a result there may be added injury to the already damaged loop of bowel. Even after the strangulation has been relieved, there may be interference with circulation because of the cramped space in which the released loop of bowel is confined.

The foregoing or other difficulties encountered at the conventional operations for strangulated hernia, require at times an upward extension through the abdominal wall of the inguinal or femoral incision, a procedure termed "herniolaparotomy." It would appear likely that, at any rate in selected instances, the immediate objective of the release and management of the strangulated bowel in operations for strangulated femoral or inguinal hernia could be more promptly achieved, and with much less likelihood of damage to compromised bowel, by means of immediate laparotomy. In my experience this method, as illustrated in the reported case, has proven entirely satisfactory in the instances in which it has been employed. An additional advantage lies in the ability to inspect directly and adequately the full extent of the visceral damage resulting from strangulation.

The question of cure of the hernia being secondary, the simple procedure

of drawing the hernial sac into the abdomen and ablating it should not be subjected to adverse criticism even if a recurrence takes place. In the case of strangulated femoral hernia, the likelihood of cure by means of this simple step, as employed in this reported instance, can be regarded as great. Much more uncertainty concerning the result will exist in the case of strangulated inguinal hernia treated by intraperitoneal ablation of the sac.

THE WILLIAM HENRY WELCH LECTURE
I. THE CONDITIONS DETERMINING CANCER¹

PEYTON ROUS, M.D.

[From The Rockefeller Institute for Medical Research, New York City]

Men never tire of discussing the relative shares of heredity and environment in making the individual what he is. The discussion has long since been extended to cancer causation, and of late very profitably; yet even today the physician can perceive only peak instances of the influence of heredity to determine cancer. And while the effect of environment is more often plain (as e.g. in pipe smokers' cancer, x-ray cancer, etc.), it is still obscured from view in most clinical histories. The resort to experimentation, however, has shown that the tendency to tumors can be bred in or out of animal families at will, and the purposeful utilization of *carcinogenic* agents to produce cancer has brought into the clear some of the most important of the conditions which determine the disease.

Prime amongst these conditions is the presence in the tissues of potentialities for tumor formation. The response to carcinogenic agents has shown that the animal body possesses such potentialities in enormous number but that they differ in character with the species and also in individuals of the same species but of different familial strains. The liability of an individual to this or that sort of growth depends first of all upon whether his tissues possess potentialities of the sort from which it may derive. Should this not be the case, the most persistent applications of carcinogens will not bring the tumor forth. The nature of the neoplastic potentialities is not yet known, but they would appear to be punctate in their occurrence in any tissue. They are familial; but whether they are actually inherited is still unsettled, this being one of the great experimental themes of the day. Certain it is that the potentialities of some strains of mice to have mammary cancer are conferred after birth, reaching the young animals by way of the mother's milk.

In order that a tumor potentiality, of whatever sort, may give rise to a growth, it must be worked upon by one or another of the many agents which we speak of as *carcinogenic*. They might better be termed *oncogenic agents*, since they act not only to change normal cells into cancer cells, but into sarcoma cells, endothelioma cells, leukemia cells, and so forth,—into all the elements in short which by proliferation form tumors in their

¹ Delivered at The Blumenthal Auditorium, The Mount Sinai Hospital, New York City, December 6, 1940.

great diversity. The oncogenic agents are notably effective in individuals with inherited tissue sensitiveness (as e.g. human xeroderma pigmentosum, in which the skin is so responsive to light that the exposure of everyday living brings on cancer).

Often the cell that has been converted into a tumor cell by a *carcinogen* becomes at once a going concern; it proliferates and a benign or malignant growth is the result. But in many cases the cell, though rendered neoplastic, requires aid if it is to assert itself. In the lack of aid it may remain latent throughout the life of the individual. While this is especially true of the cells of benign tumors, cancer cells also may require to be helped if they are to multiply into a tumor. A benign tumor cell that has proliferated, because aided may undergo secondary alteration to a cancer cell and in so doing gain greatly in abilities, becoming capable of independent growth. The help required to enable tumor cells to assert themselves need not be specific. Anything which encourages ordinary cell proliferation will do.

So dependent are some tumor cells on help and so active are they when this is afforded, that the question comes up whether certain tumors may not run a malignant course because of extrinsic influences which urge them on. The fact is well known that intercurrent infection with bacteria often enhances the malignancy of cancer. Recently it has been found that secondary infection with a virus causing cell proliferation may convert benign tumors (of unknown cause) into malignant ones and make growths that are primarily cancerous enlarge much faster and assume a different form. No doubt other agents will be discovered which can act in this way.

So many are the conditions requisite for the occurrence of cancer that it appears sporadically, despite the innumerable potentialities for it that are present in every human body. Nearly every cancer that is seen in the clinic is the end result of numerous interacting influences, consecutive and concurrent. To trace down in the individual case each and all of these responsible influences should be the aim of laboratory worker and clinician alike.

THE WILLIAM HENRY WELCH LECTURE

II. THE KNOWN CAUSES OF CANCER¹

PEYTON ROUS, M.D.

[From The Rockefeller Institute for Medical Research, New York City]

Cancer is almost always the consequence of many conditions and circumstances working together for ill. The omission of a single one of these factors may mean that the disease will not occur. In such instances the missing factor must be regarded as the determining cause of cancer. Yet though this is the case it cannot be deemed the actuating cause of the tumor. Given all necessary determining, contributing conditions, what makes a cell a cancer cell?

A great number of agents are now known which bring cancer on. They are the so-called *carcinogenic* substances. When they are listed and compared with one another, they are seen to be widely diverse in character, having nothing in common except their results. Yet despite this heterogeneity, one can often be substituted for another during the long process of eliciting cancer, or their action can be summated, facts which indicate that they work in the same way on the cells they render neoplastic. Yet they are notably non-specific. Acting upon different kinds of animals or upon those of one kind but of different familial strains, they call forth tumors characteristic, not of the carcinogen but of the species or strain. Much stress has been laid of late on the chemical relations of the carcinogens to body stuffs; and it is certain that some of the hormones, when present in excess, may bring about pathological changes in the tissues on which they act, with result that cancer arises. Yet while substances formed within the organism may call forth tumors, it does not follow that they are the intrinsic cause for the neoplastic state of the cells. Indeed the evidence is against this. All of the carcinogens except the tumor-producing viruses vanish from the growths they have engendered as these enlarge, and from the neoplastic tissue nothing resembling them which will directly produce cancer can be extracted. The generality of the carcinogens act indirectly by producing chronic tissue disturbance on the basis of which tumors may arise after a greater or less while; but they do so only if the tissue in question possesses potentialities for their formation, these differing with the species and the family, a fact brought out in the last lecture. None of the potentialities would ever become a reality were it not worked

¹ Delivered at The Blumenthal Auditorium, The Mount Sinai Hospital, New York City, December 9, 1940.

upon by one or another of the numerous agents, existing in nature or produced in the laboratory, which have the ability to evoke tumors. The agent, having done its work, disappears from the scene, and is of no more consequence.

The action of viruses to evoke tumors is of quite another kind, as shown by the known instances (which the lecturer reviewed). The neoplastic viruses are not dependent for their effects upon such tumor potentialities as the tissue may happen to possess but they provide their own, directly inducing neoplastic change of the cells upon which they act and determining the kind of tumor that results. They accompany the cells which they have rendered neoplastic as these multiply into tumors, increase in amount in association with them, go along with the tumor tissue when this is transplanted into new hosts, and can often be recovered from it in a state to produce tumors of precisely the same kind on introduction into other individuals. When they cannot be recovered, their presence can be demonstrated obliquely, as for example by serological tests. Though only a few tumor-producing viruses have been discovered as yet, they command attention as constituting the only direct causes for neoplasms that are now known. There is the more reason to consider them closely in relation to tumor etiology because of the remarkable, still largely unplumbed, capabilities of viruses in general, and the secret ways in which some are transmitted. The sporadic incidence of human tumors decisively rules out the possibility that they are consequent upon the direct transmission of viruses from individuals carrying them. As already stated, though, the liability to mammary cancer in mice of some strains is conferred on the suckling young by way of the milk; and evidence has accumulated that the animal body contains resident viruses, just as it contains resident bacteria, which ordinarily do no harm. These viruses gaining entrance to the body, perhaps shortly after birth, may persist in association with the cells of this or that organ, and produce no injury unless subjected to exceptional conditions such as the influence of the carcinogens can provide. Then at one spot or another the virus may undergo variation, cease to be a mere commensal, and act to change the cell with which it is associated into a neoplastic cell.

VITAMIN D THERAPY¹

BENJAMIN KRAMER, M.D.

[*Chief of Pediatrics, Jewish Hospital of Brooklyn*]

Historical. The story of vitamin D constitutes one of the most brilliant chapters in modern medical history. Long before the dawn of the twentieth century, cod liver oil had found a place as a valuable therapeutic agent (Ruth Guy, 1923). Early in the nineteenth century Trousseau (1872) satisfied himself, by careful clinical studies, of the specific anti-rachitic potency of this and of other fish liver oils. Nevertheless, as late as 1915 Still wrote, "There seems to be no specific virtue in cod liver oil. Any other oil will do equally well."

In 1918 Mellanby succeeded in producing rickets in puppies with a fair degree of regularity by a diet of separated milk, cereal, lean meat, sodium chloride, yeast and orange juice. To this were added a variety of oils or fats known to be deficient in fat soluble vitamin A factor. Since this diet contained an abundance of foods containing the vitamin B complex as well as vitamin C, he attributed the disease to the lack of a fat soluble factor related to, but probably not identical with, fat soluble vitamin A. The method was too laborious, time consuming and expensive for general use in the study of rickets. However, Mellanby did establish the preventive and curative value of cod liver and of egg yolk and stressed the deleterious effect of high cereal diets. Soon after both Sherman and Pappenheimer (1921) and McCollum and his co-workers (1921 to 1922) almost simultaneously and independently produced a florid type of rickets with regularity in rats. Rickets developed readily on a high calcium, low phosphorus diet which was deficient in the fat soluble vitamin contained in cod liver oil. A less severe form of the disease could be produced on a diet similarly deficient in fat soluble vitamin but containing an abundance of phosphate with minimal amounts of calcium. In 1922 McCollum and others, demonstrated the presence of a calcifying factor in cod liver oil which survived prolonged heating and aeration that completely destroyed the vitamin A factor. They called the new principle "vitamin D."

In the meantime, on the European continent Huldchinsky (1919) had succeeded in curing rickets by the exposure of infants suffering from this

¹ Lecture delivered at The Blumenthal Auditorium of The Mount Sinai Hospital on May 21, 1940 as part of the Symposium on Vitamins.

disease to ultraviolet light generated by the mercury vapor lamp. He used sunlight as well as ultraviolet light from artificial sources. Hess (1925) then repeated his previously unsuccessful experiments with sunlight alone and succeeded in curing and preventing infantile rickets. Two schools of thought regarding the etiology of rickets arose. One group led by E. Mellanby (1918, 1921) believed dietary deficiency to be the most important factor in the development of rickets. Opposed to these were another group headed by Findlay (Howland, 1923) who insisted that diet played but a minor rôle and stressed the importance of environment, as exemplified by sunlight and perhaps fresh air and exercise. In some respects the problem had become simplified. Rickets could be produced regularly by supplementing rachitogenic diets with fish liver oils or egg yolk. In rats the same measures were effective but the disease could be cured also by correcting the mineral deficiency alone. Children given cod liver oil or egg yolk either did not develop the disease or were regularly cured of their malady. Eskimos who lived in darkness all but two months of the year seldom suffered from rickets because they ate liberally of fresh fish, fish livers and fish liver oil. However, animals exposed to summer sunlight or to ultraviolet light failed to develop rickets even when fed severely rachitogenic diets. Both infantile rickets and experimental rickets could be cured regularly by exposure to light of certain wave lengths. Children of lower caste Hindus failed to develop rickets in spite of an unhygienic environment and a miserable diet, presumably because they spent the greater part of the day in the sun. High caste Brahmin women often developed osteomalacia and their children suffered from severe rickets because they practiced Purdah which necessitated the confinement of both mother and child indoors for years out of reach of the sun's rays (Hutchinson and Shah, 1938). Comparative studies of the healing effect of solar and artificial ultraviolet light and of cod liver oil showed that all agents produced the same type of healing in the bones and had the same effect upon the calcium and inorganic phosphorus concentration in the serum. The pathology of the healing process was identical with both methods of therapy. What did these two methods have in common?

The mystery was solved by the observations made independently by Hess, Weinstock and Helman (1925) and by Steenbock and Black (1924, 1925) that food substances previously devoid of antirachitic potency (vegetable oils, cereals, milk) become antirachitic when exposed to ultra-violet light. Hess and Weinstock showed that skin similarly treated becomes antirachitic. Actinic rays of wave length between $240\text{ m}\mu$ and $313\text{ m}\mu$ acted upon something in the skin to produce vitamin D, and the vitamin thus generated was absorbed and exerted an antirachitic effect. Here was the first case of a vitamin being generated in the body by the action of light energy upon a mother substance. Rickets was cured with imune-

tions of vitamin D indicating that vitamin D can be absorbed through the skin.

It was only a short and fairly obvious step from these discoveries to the fractionation of both cod liver oil and activated oils and to the discovery that antirachitic potency whether present in natural foods or acquired through irradiation resides in the sterol fraction of the material. However, cholesterol itself as well as other sterols were found to be inactive. Not all sterols became active after exposure to ultraviolet light. In fact, cholesterol when carefully purified by chemical treatment could not be activated. Only such sterols as gave an absorption spectrum showing maxima at 260, 270, 280, 282 and 293.5 $m\mu$ were activated by irradiation (Pohl, 1926). After prolonged irradiation the selective absorption disappeared and so did the potentiality for activation. This pointed to some impurity as being the mother substance. Finally, ergosterol, a sterol first isolated from ergot by Tanret and also present in yeasts and in fungi, was found to be the provitamin.

In 1930 and 1931 Askew and fellow workers at the National Institute of London, prepared crystals which showed a potency of 20,000 to 25,000 international units of vitamin D in one milligram. These crystals contained at least two inactive contaminants, pyrocalciferol and sterol "x". About the same time, Windaus, Linsert and Lüttringhaus (1932), by an entirely different method which avoided heat treatment of the material, isolated what they called vitamin D₁. This product was no more powerful than the crystals obtained previously by Askew and his co-workers and in addition contained an inert contaminant which Askew designated as sterol "x", and which Lüttringhaus later identified as lumisterin, an isomer of ergosterol, representing the first product of ultraviolet irradiation. In 1932 both groups of workers obtained crystals which subsequently proved to be pure vitamin D. This product the English workers designated as pure calciferol while Windaus and his co-workers reported it as vitamin D₂.

Since solutions of sterols from various sources (which became antirachitic after suitable irradiation) gave in each case the characteristic absorption spectrum of ergosterol, this compound was considered almost universally as the one and only provitamin and "calciferol new" or vitamin D₂ was accepted as the only form of vitamin D. One milligram of pure calciferol contained 40,000 International units (rat) of vitamin D.

Multiple Nature of Vitamin D. Even before the isolation and identification of calciferol, Bills (1935, 1939) had succeeded in activating cholesterol by chemical treatment and later produced evidence indicating that the active compound differed in its constitution from calciferol thereby indirectly establishing the multiple nature of vitamin D. Final proof of this fact, however, came through other channels.

In testing the relative value of cod liver oil and irradiated ergosterol in the prevention of leg weakness in chickens, Carrick (1939) showed that

cod liver oil when fed at the same rat unit level is much more effective than irradiated ergosterol or calciferol.

Using this method of dual assay Waddell (1934) showed that when cholesterol obtained from animal spinal cord is irradiated, the product behaves like the vitamin D of cod liver oil rather than like that of irradiated ergosterol. By means of elaborate controls Waddell (1934) proved this behavior to be due to the presence of different forms of vitamin D in the two preparations. Furthermore, irradiated skin also behaved like cod liver oil when titrated against chicken rickets. To date, Bills (1939) has described eleven different substances possessing antirachitic activity. Four of these have been isolated as chemically pure substances. The mother substances of all of these are sterols.

In 1936, Windaus, Schenck and von Werder isolated the 3-5-dinitrobenzoic acid ester of vitamin D₃ from which in 1937 Schenck obtained the pure crystalline vitamin D₃. This compound was found to be activated 7-dehydrocholesterol. One milligram assayed 40,000 rat units and was,

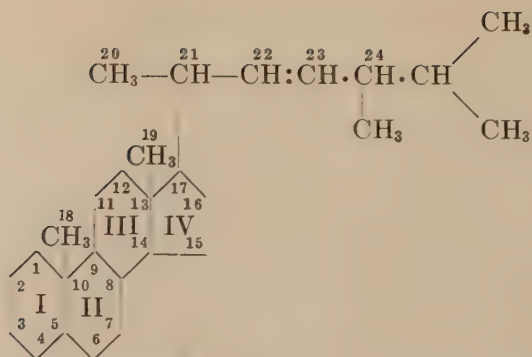
TABLE 1

Antirachitic potency of various forms of vitamin D for the rat and the chicken (after Brockman, 1937)

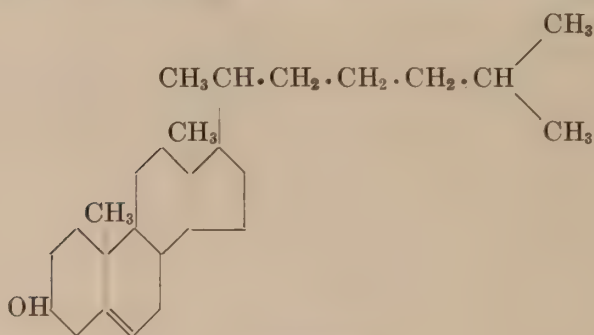
VITAMIN	DERIVED FROM	INT. UNITS PER 1 MG. (RAT ASSAY)	PROTECTIVE DOSE FOR CHICKEN RICKETS
D ₂	Ergosterol	40,000	12.0
D ₃	7-Dehydrocholesterol	40,000	0.2
D ₄	22-Dihydroergosterol	30,000	1.0
D ₅	7-Dehydrositosterol	1,200	360.0

therefore, as potent as calciferol itself. Later, the same compound was isolated from cod liver oil, tuna liver oil and halibut liver oil (Brockman, 1936, 1937). Bioassay confirmed the chemical and physical evidence of the identity of activated 7-dehydrocholesterol and the pure vitamin D isolated from fish oils (Grab, 1936). At the same rat unit level it was as potent as cod liver oil for rickets in chickens.

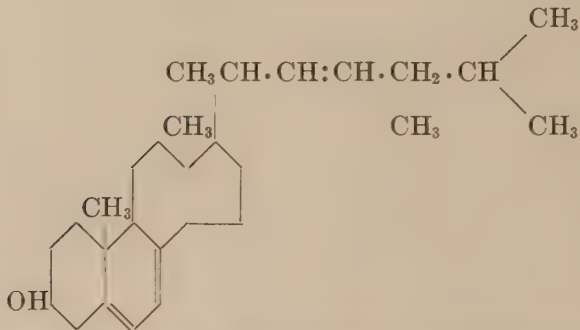
Other forms of vitamin D have been isolated. Thus, Windaus and Langer (1933) prepared vitamin D₄ as an irradiation product derived from 22-dihydroergosterol and Linsert and Wunderlich (1936) prepared 7-dehydrositosterol and from its irradiation product isolated vitamin D₅. Since sitosterol is the provitamin found in cereals it is not unlikely that activated cereals owe their antirachitic potency to vitamin D₅. The relative potency of these pure products both for the rat and the chicken are summarized in the table from Brockman. To date only calciferol has been used clinically as such. Commercial products possessing antirachitic potency owe this either to the presence of vitamin D₂ or D₃ or to both of these vitamins.



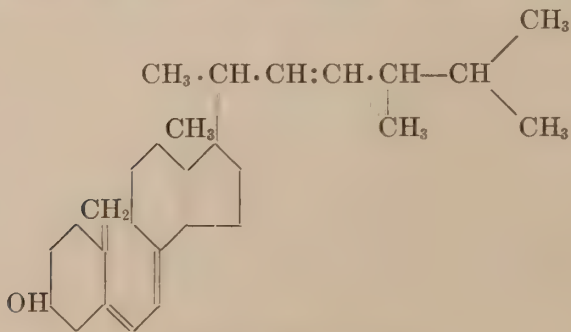
The sterol ring structure. Side chain shown as in ergosterol.



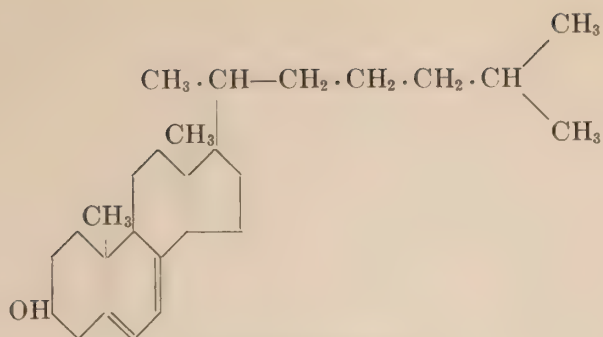
Cholesterol



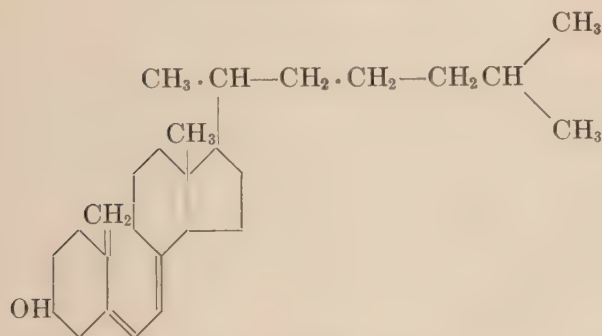
Ergosterol, lumisterol, pyrocalciferol and isopyrocalciferol.



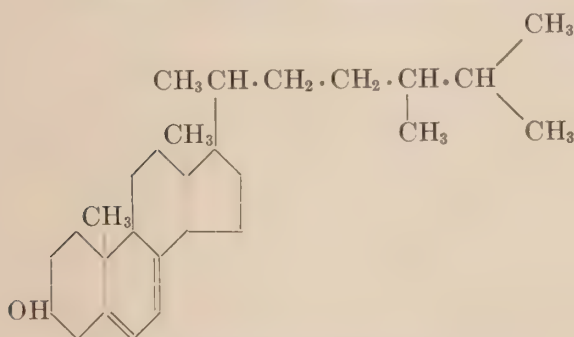
Calciferol Vitamin D₂



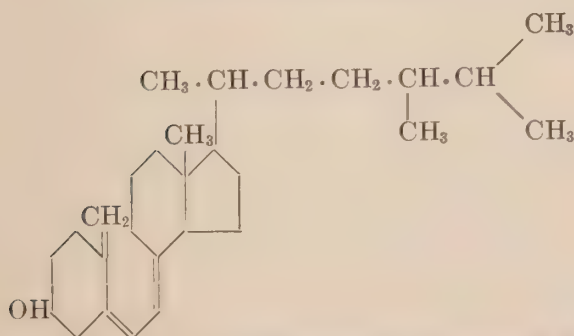
7-Dehydrocholesterol



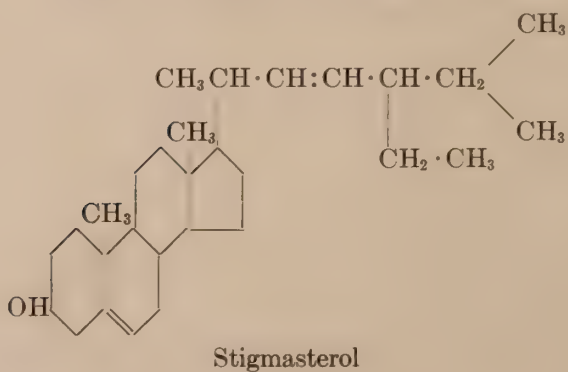
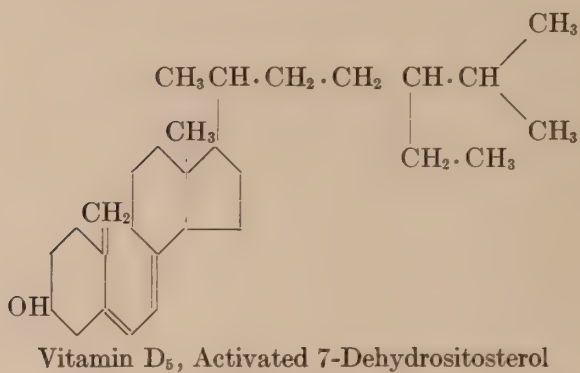
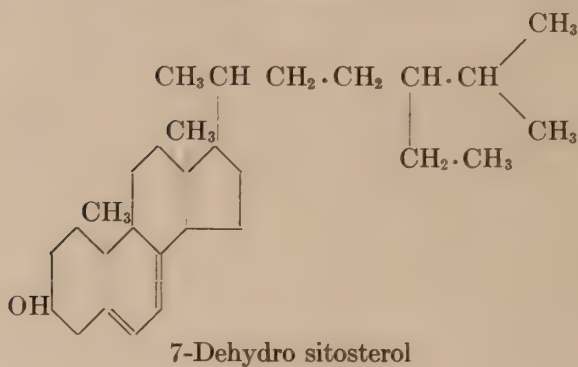
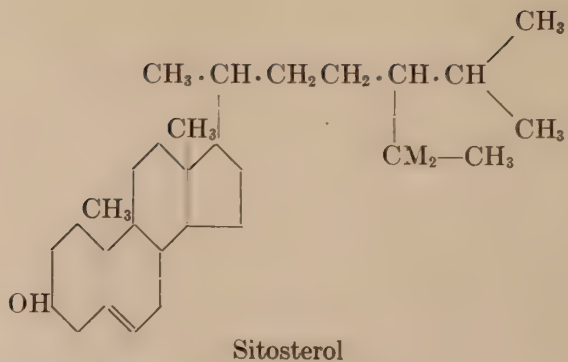
Activated 7-Dehydrocholesterol Vitamin D₃

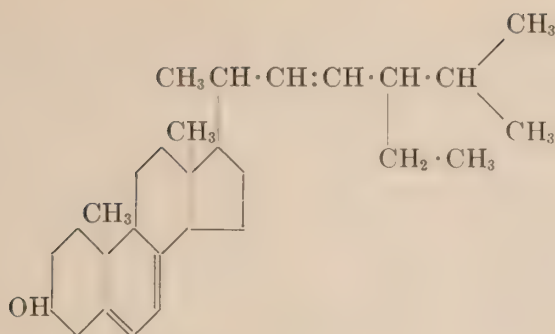


22-Dihydroergosterol



Activated 22-Dihydro ergosterol (22-Dihydro calciferol), Vitamin D₄





7-Dehydro stigmasterol

Natural Sources of Vitamin D. Among the natural sources of vitamin D may be listed fish oils including fish liver oils derived from the cod, halibut, herring, tuna and the percomorph family. Liver oils of many fish contain varying amounts of both vitamins D and A (Hume, 1936, 1937). Fish meat also contains both vitamins. Various factors influence the amount of oil in the livers and their content of vitamins D and A. By mixing oils of varying potency a fairly uniform product is made available in commerce.

Egg yolk (Branion and others, 1934) is one of the few natural foods that contain vitamin D in sufficient concentration to be therapeutically useful (Casparis, Kramer and Shipley, 1923). Neither breast milk nor cow's milk contains significant amounts of vitamin D. Cow's milk may, however, be enriched with reference to this vitamin by irradiation of the lactating animal or by feeding known amounts of vitamin D in the form of irradiated yeast mixed with a measured amount of fodder to lactating cows (Krauss and Bethke, 1937; Wyman et al, 1934). The vitamin D content of milk may be increased to about 125 U.S.P., units per quart by brief irradiation of a thin film of milk with a carbon arc lamp (Bethke et al, 1935). Such irradiation does not alter the palatability or odor of the milk and exerts only a minimal destructive action upon vitamins A and C. The vitamin D content of milk can be raised to any desired level by direct addition of pure calciferol in propylene glycol, or by homogenization of milk with cod liver oil concentrate, irradiated ergosterol or irradiated cholesterol. Such milk is usually standardized to contain 400 to 430 U.S.P. units of vitamin D. The antirachitic potency of human milk may be measurably increased by irradiating the nursing mother or by supplementing her diet with cod liver oil or vitamin D milk. (Shrader, 1934; Hess, Weinstock and Sherman, 1927; Hess, Light, Frey and Gross, 1932; Gerstenberger, and others, 1935; Kramer and Gittleman, 1933.)

Rickets. Although a vast literature has accumulated dealing with the dosage of vitamin D required for the prevention and cure of rickets, the matter has until recently been in a most chaotic state (Barnes and others,

1930). Many factors influence the severity of the rachitic process and its response to treatment. Rickets often fails to develop, or appears only in a mild form, in infants fed exclusively on breast milk although the latter contains little vitamin D, indicating that dietary factors other than vitamin D may play a part. Other factors which no doubt influence the severity of the rachitic process are heredity, rate of growth, race and color. Negro children are more frequently and more severely affected either because their diet is more likely to contain an excess of carbohydrate and is, therefore, lacking in calcium and utilizable phosphorus, or because the skin pigment absorbs the potent rays of the sun. The relative susceptibility to rickets of prematurely born infants and those of multiple births has been ascribed to lack of reserve of calcium and phosphorus, to accelerated rate of growth, as well as to imperfect absorption of calcium, phosphorus and fat soluble vitamins. The inadvertent administration of vitamin D, either through diet or incidental irradiation, complicates efforts designed to determine the minimal dose required for prevention or cure. To avoid errors resulting from such therapy a preliminary observation period of three weeks is now employed in well controlled studies. If no evidence of healing appears in the radiograph at the end of this period and blood calcium and inorganic phosphorus concentrations remain unchanged, treatment is begun. Results obtained through clinical studies in which observers have been cognizant of all the above factors are now available. The comparison of clinical potency of various preparations on the basis of the rat unit has been of much help. More exact control of other factors enumerated above as well as a clearer appreciation of the aims of therapy and of the criteria of diagnosis has brought order into the previously confused subject of dosage (Eliot and others, 1936; Park, E. A., 1940; May and Wygant, 1939).

Jeans and Stearns (1936, 1938, 1939) have summarized the aims of vitamin D therapy as follows: "Freedom from rickets or osteoporosis, good growth and development, normal values for serum calcium and phosphorus, ample retention of these elements for growing individuals and equilibrium for those fully grown."

The prevention of rickets does not represent the maximal effect of vitamin D therapy. Very small doses of vitamin D will prevent or cure the disease in the experimental animal without in many instances increasing the ash content of the bone and without producing optimal growth. Bone salts made available by solution of trabecular bone may be used to re-establish calcification in the proliferative cartilage thereby putting an end to the rachitic process (Cavins, 1924). For optimal growth and mineralization of bone not only is more vitamin D needed but also an adequate amount of calcium and phosphorus. In pregnant women an additional supply of calcium and phosphorus is needed for the growing infant while the lactating mother must have an abundant supply of these elements

and of vitamin D to insure not only a normal mineral supply for herself but in addition an adequate amount for her milk. The tendency of osteomalacia to develop or become aggravated in women during pregnancy and lactation shows that a strain upon calcium and phosphorus metabolism exists which must be fully met through liberal supply of vitamin D and of the elements upon which it works (Maxwell, et al., 1932).

Certain facts concerning the use of vitamin D in the prevention and treatment of infantile rickets seem now to be well established through the work of Martha Eliot (1936), Drake and others (1934, 1937), of many observers in this country and of Hume (1936) and her co-workers in England.

Briefly, they may be summarized as follows:

1. The rat unit of vitamin D is a measure of the antirachitic potency of a preparation in the human being. When fed at the same rat unit level, cod liver oil, calciferol, irradiated ergosterol, irradiated cholesterol (Hood and Ravitch, 1927) and various forms of vitamin D milk (Gittleman and Kramer, 1933) (Gerstenberger and Horesh, 1935) (Wyman et al., 1934) are equally effective in the prevention and cure of infantile rickets.

2. Since cod liver oil concentrate and irradiated milk owe their potency to vitamin D₃ while metabolized or yeast milk contains only vitamin D₂ it must be assumed that clinically these two forms of vitamin D are equally effective.

3. Under practical conditions a dose of between 400 and 1200 rat units (U.S.P.)² or (International)² will prevent or cure at least 90 per cent of all cases of rickets in both the normal newly born and the prematurely born infant (Davidson et al., 1934, 1935, 1937).

4. For comparative clinical assay of various forms of vitamin D, minimal doses of vitamins should be used rather than maximal amounts.

5. Massive doses of chemically pure D vitamins fed at the same rat unit level show no difference in their effect upon infantile rickets either with respect to the time of onset of healing or the time required for complete healing to take place.

6. With increasing age smaller amounts of vitamin D are required. With adequate intake of calcium and phosphorus, considerable retention of these elements may take place and a normal blood plasma level may be maintained with an intake of only such an amount of vitamin D as is present in the ordinary well balanced diet (Hunscher, Macie, et al., 1930, 1936).

² The accepted standard unit for expressing the strength of vitamin D, as adopted by the United States Pharmacopeia, is defined as the vitamin D activity of 1 mg. of the international standard solution of irradiated ergosterol, found equal to 0.025 microgram of crystalline vitamin D. This is the international unit accepted as the U.S.P. unit, except that the U.S.P. standard is a reference cod liver oil that has been assayed against the international standard.

7. Since both calciferol (vitamin D₂) and vitamin D₃ can be produced artificially in the laboratory by suitable irradiation of the proper provitamin (ergosterol or 7-dehydrocholesterol) the differentiation of a natural and an artificial vitamin D now has only historical but no practical significance.

Rickets Resistant to Vitamin D. Most children with rickets respond satisfactorily to the usual therapeutic doses of vitamin D. Some require a larger dose indicating the presence of some defect of intermediary metabolism that tends to perpetuate the rachitic state. Others are wholly refractory to vitamin D therapy. Intensive studies on several of these patients have revealed much concerning the nature of the disease and the mechanism of its development.

Prematurely born infants may require large amounts of vitamin D for protection against rickets. Shelling (1934, 1936) found it necessary in some cases to administer 10 to 60 drops of viosterol daily (1800 to 12,000 International Units) over a period of many months. The reason for this increased requirement of the prematurely born infant is not entirely clear. Rapid rate of growth, inadequate intake of calcium and phosphorus, poor absorption of these minerals as well as of fats and fat soluble vitamins all play a part.

Refractory rickets may be both chronic and severe (McCune, Mason and Clarke, 1939; Goldman and Ekstein, 1939). Cases have been reported which began in childhood and lasted into adult life. It is not uncommon for such cases to last for several years. The disease is usually associated with dwarfism and retarded growth along with gross deformities of the extremities. Radiographs of the bones reveal striking rachitic changes with bizarre deformities and marked osteoporosis. Analysis of the blood plasma regularly shows a low inorganic phosphorus concentration with a normal or somewhat low calcium level. In patients with celiac disease complicated by rickets, the serum calcium level may be below 7.0 mg. per cent and tetany is a frequent complication.

Rachitis tarda, or late rickets, (Looser, 1920; Wieland, 1914) may result from a number of factors. In some instances treatment may have been either completely withheld or given in insufficient amounts. Such cases are quite unusual today. In most cases the reason is not obvious. Defective absorption of calcium, phosphorus and of vitamin D may play a part. A careful study of the patient often reveals evidence suggestive of endocrine imbalance or a disturbance of the acid-base mechanism. Certain specific renal functions may be disturbed although the usual functional tests reveal no abnormalities. Occasionally, evidence of gross liver damage may be obtained. In some, as yet imperfectly understood, manner this affects the severity of the disease and its response to antirachitic therapy. In celiac disease, defective absorption of calcium, phosphate and vitamin D are doubtless the major factors. When concentrated prepara-

tions of vitamin D are administered in a dose of 60,000 to 100,000 units daily, healing soon begins (Parsons, 1927). Parenteral administration of vitamin D is even more effective. In addition the celiac condition must receive appropriate dietetic therapy. In some cases a chronic acidosis complicates the rachitic condition (Boyd, 1929; Bornscheuer, 1931; Stearns and Warweg, 1935) and tends to perpetuate the disease unless corrected by a supplement of alkali or the administration of an alkaline ash residue diet in addition to large doses of vitamin D. In other instances healing is initiated by the administration of toxic doses of the same vitamin 1,000,000 to 1,500,000 units daily for a few days (Albright, Bloomberg and others, 1938). Later, the dose may be reduced to safer levels and healing will continue to completion. Liver damage may be a factor in maintaining the refractory state, as in children with severe rickets described by Gerstenberger (1933) and Thoenes and Gunson (1936), and in one case of fatal rickets with a large hepatoma reported by Farber (1937). In some instances the so-called "hepatic rickets" was complicated by anomalies of the bile passages which resulted in the exclusion of bile from the gastro-intestinal tract. No doubt the absence of bile interferes with the absorption of fats and indirectly, perhaps, of fat soluble vitamin D. In these patients, parenteral therapy is more effective than when medication is administered by the oral route. Albright and his co-workers (1937, 1940) described a patient with chronic rickets, dwarfism, nephrocalcinosis and chronic acidosis associated with chloride retention. This patient had marked rickets with decalcification of all the bones although areas of calcification were widespread in the kidneys. Healing of the rachitic state was initiated only after the administration of large doses of vitamin D supplemented with a solution of citric acid and sodium citrate which corrected the chloride acidosis in the blood. The titration of the blood for vitamin D by bioassay has been helpful in following the absorption of the vitamin in cases of refractory rickets.

DeToni (1933) described a new form of rickets in a child (Warkany, 1930) whom he had observed for several years. The patient had a glycosuria of varying intensity which was independent of the amount of carbohydrate ingested. The serum calcium was normal while the phosphorus was low. The phosphatase level was increased. The case differed from "renal rickets" in that there was no evidence of renal damage. The urea and non-protein nitrogen in the blood were normal, the blood pressure was normal and the ophthalmoscopic examination was negative. The specific gravity of the urine varied within wide limits. The patient showed typical clinical signs of rickets including a "rachitic rosary," enlargement of the wrists and ankles, "knock knees" and tenderness on pressure over the bones, dwarfism and finally inability to walk. There was little evidence of renal damage. Albuminuria was present but no casts, blood, or pus could be demonstrated. Roentgenographs of the bones showed

marked osteoporosis with typical rachitic changes and spontaneous fractures. The writer was impressed by the difference between this disease and cases previously described as "renal rickets" and by its failure to respond to large doses of vitamin D (Debre et al., 1934; Schlessinger, 1931; Ullrich, 1929).

Fanconi (1936) described three cases, reported two additional cases from the literature, and made some elaborate metabolic studies. He showed that although the usual tests for kidney function revealed no evidence of renal damage and the specific gravity of the urine varied over very wide limits indicating normal diluting and concentrating function of the kidneys, there was obviously a marked disturbance in the acid base regulatory function of the kidneys as well as a defect in intermediary metabolism. The former expressed itself in a fixation of the urinary pH which did not drop below pH 6.5 even after administration of acid producing salts, while the latter expressed itself first as a glycosuria which varied in intensity, and secondly, in the form of a marked increase in the amount of organic acid in the urine. This excess was as a rule not due to ketone acids. In view of the inability of the kidney to excrete an acid urine, there was a wastage of base including calcium in the urine and a large amount of phosphate buffer was made available for the neutralization of inorganic and organic acids. This explains the persistent hypophosphatemia. Blood serum calcium level was usually normal or slightly reduced. Blood sugar curves may be of diabetic character. One of Fanconi's cases showed nephrotic changes in the renal tubules at autopsy. Gittleman and Pincus (1940) have shown that the administration of glucose to such a patient may fail to produce the usual rise in the respiratory quotient. Fanconi was unable to bring about healing when sodium bicarbonate or sodium citrate were administered along with vitamin D. Pincus and Gittleman similarly were unsuccessful with the citric acid sodium citrate mixture described by Shohl (1937). Guild, Pierce, and Lilienthal, Jr. (1937) reported a similar case in a seventeen months old girl. Classical clinical signs of rickets were present, with marked roentgenographic evidence of both rickets and osteoporosis. The blood serum calcium was 8 mg. per cent while the inorganic phosphorus was 1.3 mg. per cent. The phosphatase level was 49.9 units. A glycosuria was present while the renal threshold for sugar was low, i.e., a little less than 65 mg. per 100 cc. of blood. Twenty to thirty grams of sugar appeared daily in the urine. A sugar tolerance test showed a rapid rise of blood sugar to 180 mg. per cent followed by a fall within two hours to 50 mg. per cent. The blood carbon dioxide combining power was about 30 volumes per cent. Although twenty times the normal amount of organic acid was excreted in the urine the pH averaged only 6.5.

Single Massive Dose Therapy. With the development of highly potent concentrates of vitamin D, it was thought possible to accelerate the healing

process in rickets and to insure protection for several months by the oral or parenteral administration of a single large dose. Since rickets tends to develop in the fall and winter or to become active at that time, only to subside in the summer, it was thought likely that such a large dose given in the fall would insure protection for the entire winter period. Studies conducted in out-patient clinics indicate that many mothers fail to cooperate because the antirachitic agent must be administered daily over a period of many months. It is to this failure that we must attribute in large part the occurrence even today of many mild and moderately severe cases of rickets. The fear of hypervitaminosis has been a deterrent in the adoption of the single massive dose treatment for general use.

In 1928, Vollmer (1930, 1938, 1939) treated six rachitic infants with from 70 to 120 mg. of irradiated ergosterol administered in several doses. Some of this was administered subcutaneously and some orally. The results appeared to be satisfactory. Reports of hypervitaminosis soon appeared in increasing numbers, however, even with the use of ordinary therapeutic doses of the early preparations of irradiated ergosterol. When these early preparations were found to contain toxic sterols, the single dose method was promptly abandoned (Dale and his co-workers, 1932; Ham and Lewis, 1934).

With the preparation of the pure vitamins D_2 and D_3 by Windaus (1931) and his collaborators, the possibility of using such a large single dose therapeutically was again brought forward and has been explored by Harnapp (1936, 1937, 1938), Schirmer (1937), Bischoff (1937), Vollmer (1928, 1939, 1940), and more recently by Ström (1939), Amy Van Ormondt (1937, 1939), Brockman (1937, 1938), Broulke (1937), Hartenstein (1939), and others.

This method of treatment is based upon the observation (Heyman, 1937) that when a single large dose of viosterol in oil, representing 200,000 U.S.P. units, is given to rabbits by stomach tube the vitamin may be demonstrated in the tissues and blood plasma of the animal for a variable period after administration. In brain tissue it can be detected by bio-assay two weeks after ingestion. It is still present in the skin after six to eight weeks, in the lungs and kidneys after nine weeks; and in the liver and blood plasma at twelve weeks.³

The treatment as advocated by Vollmer consists in the administration of 500,000 to 600,000 units of vitamin D either by mouth or by intramuscular injection in a single dose. Occasionally, this may be administered in two equal doses or the dose may have to be repeated in three or four months. Vollmer maintains that such treatment initiates healing sooner than when repeated small doses are administered. The mood of the child

³ Vollmer administered several massive doses of vitamin D to a child shortly before death and was able to demonstrate only about 20 units of vitamin D per 100 gm. of liver. Other tissues did not contain demonstrable amounts of the vitamin.

improves within one to three days, craniotabes disappears in two to three weeks, and the inorganic phosphorus of the serum returns to normal within four days. Hyper-normal values of serum inorganic phosphorus may appear but decline to a normal level within four weeks. Serum calcium, when low, reaches or exceeds the normal value within two to four days. Evidence of fresh calcium deposition in the proliferative cartilage appears in less than twelve days and healing may be complete in less than six weeks.

This form of therapy seems to be particularly valuable in infantile tetany. Convulsions cease promptly after the administration of a single large dose of 600,000 international units, without any other therapy. The serum calcium may reach a normal level within sixty hours to ten days. Single massive dose therapy is effective in cases of neonatal tetany which are often quite resistant to calcium chloride. Abnormal electrical reactions may disappear in a few days or persist for one or two weeks.

Because this method of treatment accelerates calcification of the rachitic cartilage and bone, its use has been advocated in thoracic rickets where there is danger to life from the rachitic process itself. Its use has also been advocated in pneumonia or whooping cough complicating rickets where prompt hardening of the thoracic cage is essential to enable the chest to resist changes in atmospheric pressure incident to respiratory effort.

Vollmer found no toxic symptoms in 150 or more infants treated in this way. Schirmer could find no abnormal electrocardiographic changes following the administration of similar large doses of the vitamin. On the contrary, the prolongation of the Q-T interval frequently seen in tetany often disappears promptly after massive vitamin D therapy. Vollmer believes that doses even larger than 600,000 units may represent the optimum in infants older than three months. More recently, he has reported equally good results in both experimental and clinical studies where the material was given by subcutaneous injection. Satisfactory results with this type of treatment in the prevention of rickets have also been reported in the prematurely born infant by Carl Zelson (1940). Premature infants remained free of rickets for two to six months after a single large dose. No unfavorable symptoms were observed.

The fact that the inorganic phosphorus occasionally rises to abnormally high levels and that the calcium more frequently follows a similar course, indicates the necessity for caution in the general adoption of this method of therapy. Rickets is seldom a fatal disease and a treatment which involves the risk of hypervitaminosis should not be used except where special indications justify such a procedure. When tetany threatens or is actually present or where thoracic involvement menaces the life of the patient or there is danger of severe rickets developing through neglect, the use of this method of treatment may at times be justified. It is ad-

visible, however, to wait until further opportunity has been given to more fully explore the effects of such large doses of vitamin D upon human tissues before recommending its adoption for routine use. The fact that harm may follow the use of large doses and that even fatalities have been seen after amounts far less than the level usually considered toxic should serve as a warning. Kerr (Freyberg and others, 1936) has reported a fatality in an adult following the accidental administration of a total of 2,300,000 international units of vitamin D over a period of eighteen days. The early symptoms were vomiting, nausea, diarrhea, polyuria and anorexia. The patient died in coma. Albright and his co-workers have reported toxic symptoms following the administration of 1,000,000 international units daily for several days. Increased excretion of calcium in the urine along with calcium crystals and calcium casts were present even in the absence of hypercalcemia. Ross and Williams (1939) have described hypervitaminosis in children treated for a period of several months with 20,000 to 40,000 units of vitamin D daily. Hypercalcemia of 18 mg. per cent with a normal inorganic phosphorus in the blood was present. Areas of increased density were present in the provisional zone of calcification in the long bones. Proximal to these there were areas of rarefaction and proximal to this there was a zone of increased density. There was generalized periosteal thickening with a dense outer layer and a rarefied zone between this and the dense bone. Malnutrition, weakness, muscular hypotonia, peripheral facial palsy and anemia were present in one case and evidence of renal damage in two cases. There were two deaths and two recoveries. All the patients had anorexia, vomiting and loss of weight. Such cases must be exceptional. Grayzel, Shear and Kramer (1931) have administered 60 to 100,000 units daily as irradiated ergosterol (Viosterol) over a period of months, to children without any demonstrable deleterious effect. The concentration of calcium and serum inorganic phosphorus remained normal. No abnormal urinary findings were noted and appetite and weight gain were all the same as in a control group of children. It must, however, be borne in mind that certain children may be unusually susceptible to vitamin D. When large doses of this vitamin are being administered, repeated determinations of serum calcium and inorganic phosphorus should be performed and, from time to time, treatment should be withheld for one or more weeks to avoid a cumulative effect of the high dosage.

Treatment of Miscellaneous Conditions. Vitamin D prevents and cures rickets and tetany. Within the last decade attempts have been made to extend its field of usefulness. It has been tried in the treatment of intestinal, bone and lymph node tuberculosis in the hope of accelerating the calcification of such lesions (Crimm, Grayzel, and others, 1931, 1932). Its use in the treatment of arthritis (Reed and others, 1939) grew out of a chance observation in which improvement (Vrtaik, 1936; Farley, 1937)

of a complicating arthritis occurred in an allergic patient who was receiving large doses of vitamin D. Acne vulgaris, seasonal hay fever (Rappaport, 1937; and Reed, 1939) infectious and atopic asthma and urticaria, calcinosis universalis and psoriasis have also been similarly treated (Ceder and Zon, 1937; Brunsting, 1938). Vitamin D therapy (Cornbleet and Struck, 1937) has been used either to supplement accepted methods or as the sole method of therapy when other methods had proven ineffective. The dose of vitamin D used in most of these cases varied from 40,000 to 250,000 units daily. The higher dose is the one usually used. Conservative observers are in agreement that the results are not superior to those obtained by standard methods. The literature has been reviewed by Reed and his co-workers. It seems doubtful whether the results so far obtained justify the use of a method which possesses so much potentiality for harm.

In lead poisoning (Sobel and his co-workers, 1940) the metal may be demonstrated in the blood plasma and abnormal amounts are often present in the stools and urine. Lead salts are deposited in the bones particularly where active bone growth is taking place. Deposition and mobilization of lead are influenced by the same factors which affect deposition and mobilization of calcium salts. The influence of vitamin D depends upon whether lead salts are still being ingested. When lead salts are still available in the gastro-intestinal tract the administration of vitamin D favors their absorption and raises the lead level in the serum and whole blood, and the symptoms of lead poisoning are aggravated. Lead encephalitis is a frequent complication. When lead is no longer being ingested vitamin D tends to maintain a high concentration of serum inorganic phosphorus and lead concentration in the plasma is reduced while lead salt deposition in the bones is increased (Rappaport and Rubin, 1937; Sobel, and others, 1938).

"A.T.10" (*Anti-Tetany*) (*Dihydrotachysterol*). The formation of vitamin D from pure ergosterol by irradiation does not take place by simple conversion of one substance into the other. Several by-products are formed in the irradiation process. Some of these are inert while others are definitely toxic. The order in which these compounds appear is as follows: ergosterol, lumisterol, tachysterol, calciferol, toxisterol (Sub. 248), suprasterol I and II. The form of vitamin D developed is the same no matter what form of radiant energy is used but depends upon the chemical structure of the provitamin. However, the relative amount of active, inactive and toxic material formed depends upon the wave length of light used, the nature of the solvent and the duration of the irradiation. Earlier preparations produced symptoms of hypervitaminosis even when fed in therapeutic doses. This was found to be due to toxic sterols which had a marked hypercalcemic effect and at times produced pathological calcification, but had little antirachitic action. Several of these have been iden-

tified. Dihydrotachysterol is a compound whose virtue lies in the fact that it exerts a parathyroid-hormone-like action when given by mouth. It has been designated as a "calcinosis factor" because it produces hypercalcemia and as "A.T.10" because of its anti-tetany action.

The difference between the action of "A.T.10" (anti-tetany) parathyroid hormone and vitamin D has been summarized by Albright (1938). Parathormone has no effect on the absorption of either calcium or phosphorus but mobilizes calcium salts from the bones. It facilitates the loss of phosphate in the urine and thus keeps the plasma inorganic phosphorus concentration at a low level or reduces a previously high blood plasma phosphorus enabling the calcium level to rise to a normal value. In toxic doses it produces a hypercalcemia which may result in metastatic calcification or in a fatality. After repeated injections the body becomes refractory to the hormone. Parathormone may be ineffective in tetany complicating rickets because of a dearth of mobilizable calcium in the bones (Hoag, 1927). Vitamin D improves the absorption of both calcium and inorganic phosphorus from the gastro-intestinal tract and helps to deposit bone salts in the cartilage matrix and osteoid tissue. The blood serum calcium and phosphorus are restored to a normal level. With toxic doses hypercalcemia is very common while hyperphosphatemia is occasionally encountered. While more phosphate appears in the urine, vitamin D actually tends to conserve phosphorus by improving resorption of phosphate from the proximal convoluted tubules of the kidney (Harrison and Harrison, 1941). "A.T.10" occupies an intermediate position in its effect upon calcium and phosphorus metabolism. Absorption of calcium is improved and hypercalcemia may follow, but bone salt deposition does not occur because hypophosphatemia persists. Neither "A.T.10" nor parathormone preparations should be used in the presence of active rickets since either substance may aggravate the disease (Harnapp, 1935).

Theoretically, "A.T.10" is the chemical of choice for the treatment of postoperative or idiopathic hypoparathyroidism (Holtz, 1934; Reider, 1933). When administered in dosage of 1.0 to 5.0 ml. of the oily solution along with 2 to 4 gms. of a calcium salt, either as the lactate, gluconate or chloride, it quickly restores the hypocalcemia to a normal serum calcium level without raising the inorganic phosphorus level. The patient does not become refractory to the drug as with parathormone. The dose may subsequently be reduced to 1 to 3 cc. every other day or even once a week. Treatment must be controlled by frequent determinations of serum calcium. Some recent studies indicate that good results may be obtained in the treatment of hypoparathyroid tetany with vitamin D when administered along with diets that are low in phosphorus to which calcium salts have been added. Hypocalcemia is corrected with no elevation of plasma inorganic phosphorus, and the symptoms of tetany disappear. In view of the toxicity of dihydrotachysterol, the uncertainty

regarding dosage and the fact that good results in the treatment of post-operative tetany may be obtained with vitamin D, calcium salts and low phosphorus diets it is not surprising that the use of dihydrotachysterol has so far been confined to a few clinics (Freyberg, 1936).

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THE ORGANIZATION OF THE BLOOD BANK AT THE MOUNT SINAI HOSPITAL¹

OBSERVATIONS AND RESULTS FROM JUNE 1938 TO JUNE 1940

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With the introduction of blood groups by Landsteiner (1) and Von Decastello and Sturli (2) at the beginning of the century, and the corroborative reports of Jansky (3), Moss (4), Ottenberg (5), and Ottenberg and Kaliski in 1913 (6), blood transfusion was definitely established as a safe and effective therapeutic procedure. As is usual with any new treatment or method, a few years passed before the therapeutic value of blood transfusions was recognized. Whereas the early transfusions of artery to vein, developed by Crile (7), required the services of a skilled surgeon, direct insertion of needles into the vein of recipient and donor by Lindeman (8), and the eventual use of the Lewisohn citrated blood method (9) so simplified the procedure that transfusion has become a routine and easily performed therapeutic measure.

With simplification of the method, the number of transfusions given has increased steadily. At The Mount Sinai Hospital in New York, an institution with approximately 500 ward beds, the number of transfusions rose from a few each week during the years 1915 to 1920 to as many as 100 per month during 1937. This figure might have been even greater were it not for the fact that the financial burden to the hospital, especially during the period of the depression, became too great to keep up with the demand for transfusions. Although in many instances family donors were available, these could not be employed because their blood was not compatible with that of the particular patient. The blood bank appeared to offer a solution to this problem since blood could thus be stored and made available for transfusions at all times.

The use of stored blood was suggested in 1915 by Weil (10) who was able to transfuse animals with blood stored in the icebox for a period ranging from overnight to one week. Robertson (11), however, was the first to demonstrate the efficacy of stored blood in human beings. Such blood was kept for only a few days and was employed in emergencies during the first World War.

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* With the technical assistance of Drs. J. Churg, B. Pedersky, M. Volterra, and P. Greenberg.

The impetus to the popular use of stored blood is the result of recent work by numerous Russian investigators. Shamov (12), in 1926, transfused exsanguinated dogs with blood removed from dogs as long as six hours after death and subsequently stored for a number of days. The results of his experiments were exceptionally good. He showed, moreover, that such blood had normal oxygen-carrying capacity and its administration was followed by a rise in hemoglobin. In 1930, Yudin (13), using Shamov's experiments as a basis for similar work in human beings, successfully transfused fresh, citrated cadaver blood into patients. Later, cadaver blood, stored for as long as three weeks, was found to be effective.

These interesting results were carried a stage further by the finding of spontaneous fibrinolysis by Skundina in 1935 (14). This spontaneous liquefaction of the coagulum occurs in blood withdrawn from persons who have died suddenly and is probably due to a proteolytic enzyme released into the blood after death.

The use of cadaver blood was not popular except in certain restricted centers, and this circumstance led to the employment either of stored blood obtained from volunteer donors or, in certain instances, of placental blood.

The first blood bank was organized in Leningrad by Filatov and Depp in 1932 (15). The transfusions were limited in amount to 200 to 400 cc. Small transfusions of 250 cc. of blood varying in age from 2 to 18 days were given in a small series of 43 cases. Chills occurred in only five. Glucose-citrate mixtures employed as anticoagulants caused 50 per cent reactions. Other blood banks were started in Chicago, Philadelphia, Memphis, and shortly thereafter in New York City. All these reports confirmed the favorable opinion of Fantus (16) and of Fantus and Schirmer (17).

During this period (1937 to 1939) studies were being made in our laboratory on the efficacy of stored blood transfusions in comparison with fresh blood transfusions. At the same time, experimental observations were carried out on the morphological and chemical changes in stored blood. These results, as well as the *modus operandi* of the blood bank, form the basis of this article.

Procedure. Blood for the bank is obtained as a voluntary donation from friends and relatives of patients in need of transfusion. These donors are given appointments to appear at the phlebotomy sessions which are held three times a week at stated hours. In order to concentrate all procedures in one unit, a special seven-bed ward with an icebox capable of storing 150 pints of blood at 2 to 4°C. was made available. Donors are registered, typed, and examined before phlebotomies are performed. The rapid slide method of typing (Coca) is used. High titre serum furnished by the Blood Transfusion Betterment Association is employed. Questionable groupings, which occur rarely, are checked by the Schiff Modification of the Landsteiner tube method (18).

After a brief experimental period, during which various types of contain-

ers were tested (Erlenmeyer flasks, Patented closed-system flasks), it was decided that the simple open-system with the use of a quart-size Mason jar was most satisfactory. This container is the least expensive, is easiest to clean properly, and occupies little space in the icebox (fig. 1). A critical analysis of our results over a period of two years has served to confirm our decision concerning the use of the open-system.

The phlebotomies are performed in the following manner: After surgical preparation of the arm with iodine and alcohol from axilla to wrist, and careful draping of the arm, a 13 to 15 gauge Luer needle with an 8 inch latex rubber tubing attachment is inserted into the vein through a pro-cainized skin area.

The blood is collected in a Mason jar to which has been added 50 cc. of 3.8 per cent sodium citrate solution. In addition, blood is collected in two

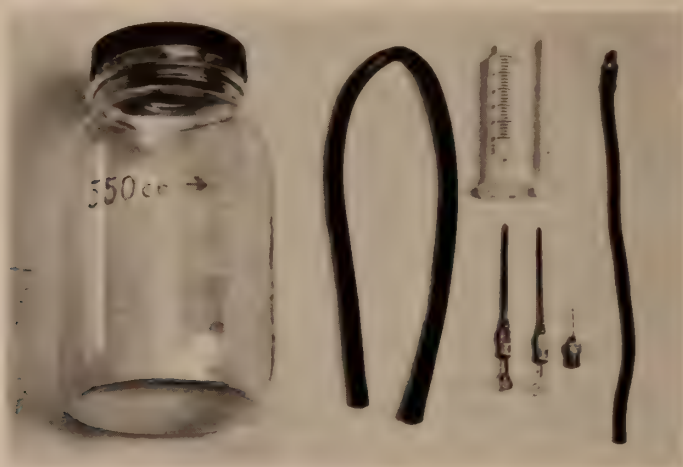


FIG. 1. Photograph of apparatus

small test tubes, one of which is attached to the jar for subsequent use in cross-agglutination or matching. The second tube is sent to the serology department for the Kahn test. Bloods giving a positive Kahn reaction, instead of being discarded, are sent to the bacteriology laboratory for use in culture media. If blood has not been used for transfusion within 10 days, the plasma is siphoned off, diluted with an equal volume of physiological saline solution, and stored for use as an infusion in the treatment of shock and nephrosis, and in pre- and postoperative supportive therapy.

When the blood is dispensed, the pilot tube is removed and sent to the laboratory, where it is retyped and cross-matched with the patient's blood. The jar of blood is removed from the icebox and allowed to stand at room temperature, awaiting the report on compatibility. No other method of warming the blood is advised. Although Vaughan (19) and Riddell (20) have advised warming the blood to 40°C., we feel that this procedure is

not only unnecessary and time-consuming, but may lead to serious consequences, as Baker (21) has reported. On the other hand, DeGowin, Hardin, and Swanson (22) have shown that the administration of cold fluids, even at a rapid rate, has little or no effect on the circulatory system and the general condition of the patient. Lewisohn and Rosenthal (24) and Goldhamer (23) have offered confirmatory reports. Before use, the blood is filtered through two layers of washed gauze into special 500 cc. beakers which have been previously autoclaved for this purpose. It is then poured directly into the open gravity tube and given at any rate desired by means of the intravenous drip method (Hyman and Hirshfeld (25)). It must be emphasized that the cleansing of the apparatus, as described by Lewisohn and Rosenthal (24) and stressed by Riddell (20) and Fantus and Schirmer (17), is especially important in reducing reactions to a minimum. In brief, this method requires that all apparatus used for intravenous infusions, glassware, rubber tubing, and needles, be washed with tincture of green soap and rinsed with tap water. This material is next boiled for 5 minutes in 0.1 per cent sodium hydroxide, rinsed in distilled water, packed into bundles, and autoclaved. The sodium citrate solution (50 cc. of 3.8 per cent) is prepared each week by the hospital pharmacy. Freshly distilled water and chemically pure sodium citrate are used. The solution is filtered and autoclaved in two ounce, capped bottles immediately. After one week, all unused citrate solution is discarded.

In instances when it is felt that a particular patient may require a transfusion during or following an operation, the compatibility test is performed in advance, so that the blood may be given on short notice without delay. In these cases only a portion of the blood from the pilot tube is removed for the cross-matching; should the blood be returned unused to the active portion of the bank, enough blood would thereby be left in the pilot tube for later cross-matching against serum of another patient.

Analysis of results. In order to determine the value of stored blood, numerous studies were made on: 1) the effect of transfusion of stored blood of varying ages on recipients; 2) the morphological, bacteriological, and chemical changes in the stored blood itself. Patients were examined before and after transfusion for changes in hemoglobin, red blood cell count, hematocrit and icterus index, and a careful analysis of the patient's symptoms and temperature chart was made to determine the existence of even the slightest reaction. On the stored blood itself the following studies were made at regular intervals: complete blood count, fragility test, prothrombin time, pH, oxygen-carrying capacity, concentration of glucose, lactic acid, and antibody content. Urobilinogen determinations of the urine and stool following the transfusion of blood of various ages were completed. They form the basis of a separate report, but they will be briefly summarized here.

The principal indications for transfusion are blood loss, -medical or

surgical,—shock, infection, anemia, or any combination of these conditions. Appraisal of the value of transfusion given for any of these reasons may be judged by the clinical response as well as by the changes in the blood count. Since the introduction of transfusion with stored blood, doubt has arisen whether or not the beneficial effect of this type of blood is as great as that of fresh blood. In an effort to throw some light on this problem, a study was made of 240 transfusions of stored blood, with reference to changes in the hemoglobin, red blood cell count, and hematocrit index at definite intervals after transfusion compared with pre-transfusion values. Because certain cases receiving stored blood were found to have developed transient icterus shortly after transfusion, a study of the icterus index was undertaken at the same time (table 1, fig. 2).

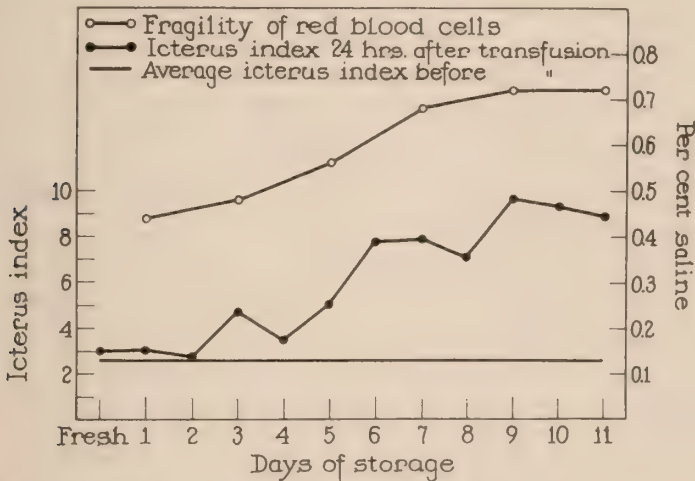


FIG. 2. Average change in resistance of stored red blood cells to hypotonic saline. Average rise in icterus index 24 hours following transfusion of blood stored for periods varying from 1 to 11 days.

Methods. Analyses were made on oxalated venous blood, to which 1 drop of 20 per cent potassium oxalate solution was added to each 5 cc. of blood. Specimens were taken from the patients before transfusion and 1, 3, and 8 days after transfusion. In some cases in which multiple transfusions were given this routine could not be followed and such patients were studied daily.

The hemoglobin determinations were done by means of the Klett photoelectric hemoglobinometer and the results were determined in grams of hemoglobin per 100 cc. The red blood cell counts were carried out in the usual manner, Hayem's solution being used as the diluent. The counting chambers and pipettes were standardized equipment. The hematocrit determinations were made in Wintrobe tubes which were centrifuged for

45 minutes at 1200 revolutions per minute. In the determinations of the icterus index, the modified acetone method was used (26).

Results. The 240 transfusions studied were administered to 115 unselected patients. Sixty-three patients received single transfusions and the remaining fifty-two patients received from two to eleven. The age of the stored blood varied from 1 to 11 days in 220 of the transfusions, fresh blood being used in the other twenty (table 1).

Table 1 shows average results in the full series of 240 transfusions classified according to the age of the blood when dispensed. Transfusions with blood of all ages showed a rise in the blood figures 24 hours later. The blood examinations made 3 days following transfusion likewise showed a further rise over the pretransfusion level, except in the 11-day-old blood, whereas the 8 day observation revealed a still greater rise in some groups and a slight drop in others. The transfusions of fresh blood gave the

TABLE 2

Average change in hemoglobin (grams per cent), red cell count, and cell volume in various conditions following transfusion of stored blood

NUM- BER OF CASES	DIAGNOSIS	BEFORE TRANSFUSION			ONE DAY AFTER TRANSFUSION			THREE DAYS AFTER TRANS- FUSION			EIGHT DAYS AFTER TRANS- FUSION		
		Hemoglobin	Red cells	Cell volume	Hemoglobin	Red cells	Cell volume	Hemoglobin	Red cells	Cell volume	Hemoglobin	Red cells	Cell volume
85	Infection	11.1	4.07	31.5	11.6	4.28	33.5	11.5	4.52	36.5	9.8	3.82	29.5
40	Surgical	8.1	3.94	31.5	11.2	4.27	32.5	11.0	4.3	32	11.3	4.6	33
36	Malignant	7.7	3.18	26	9.6	3.7	29	9.4	3.8	29	9.2	4.4	30
35	Bleeding	6.8	2.96	21	7.3	3.36	22	8.6	3.5	26	9.4	3.73	30
44	Blood dyscrasia	6.5	2.32	20	7.7	3.2	23	7.7	3.3	23	7.9	3.42	30

greatest rise of any group, but otherwise there was no correlation between the age of the blood and the height of the rise. The reason for this apparent inconsistency is probably due to the type of case making up a particular group.

An analysis of results according to diagnosis is presented in table 2. The cases were divided into five main diagnostic groups for this purpose, namely,

1. *Infection* (85 transfusions) sepsis, pneumonia, subacute bacterial endocarditis, rheumatic heart disease.
2. *Surgical* (40 transfusions)—pre-operative and postoperative supportive treatment.
3. *Malignancy* (36 transfusions)—carcinoma, sarcoma, of any type.
4. *Bleeding* (35 transfusions)—acute or chronic hemorrhage.
5. *Blood dyscrasia* (44 transfusions)—leukemia, thrombopenic purpura.

An average result of the 85 transfusions given for infection showed a very slight rise in hemoglobin, red blood cell count, and hematocrit in the first three days after transfusion and a drop to below the initial figures by the eighth day. The bulk of the transfusions in this group were administered to patients with subacute bacterial endocarditis, who were, at the same time, being given radiotherapy, physiotherapy, and sulfanilamide. It is felt that these other forms of therapy detracted from the full benefit afforded the patients by the transfusions. All the other groups, however, showed a rise during the period of observation which was well maintained throughout. The greatest rise was found in Group II (surgical cases).

The study of the change in the icterus index in the full group of 240 transfusions (table 1, and fig. 2) showed a consistent increase in the index 24 hours after transfusion. Blood stored for 5 days or less produced minimal increase, blood aged 5 to 8 days, a somewhat greater increase, and that stored more than 8 days the most marked change. In all groups it was noted that the icterus resulting was transient in nature, and a return to normal figures was practically universal by the third day (table 1).

The observations in our series of stored blood transfusions revealed exceedingly favorable results. The majority of patients so transfused showed a rise in the blood count and hematocrit value immediately after the procedure which was well maintained throughout the period of observation. It is true that by the eighth day there was a slight drop from the initial post-transfusion rise in most cases, but Sibley and Lundy (27), in a study of fresh citrated blood transfusions, found a similar drop after one week.

Blood stored up to the tenth day produced comparable results in our cases insofar as the rise in hemoglobin was concerned, although this rise was not quite so great as in the control series of fresh blood transfusions. The various diagnostic groups responded well except in the cases of infection, in which other forms of therapy influenced the results.

Transient icterus after the use of stored blood has been observed by Grosdov (28) and Yudin (29). The latter observed jaundice in five cases transfused with cadaver blood which was between two and three weeks old. This blood contained no anticoagulant. He concluded that the blood should be administered before it has reached ten days of age. Fox (29) reports an incidence of 14 per cent post-transfusion jaundice in patients receiving stored blood, contrasted with an incidence of only 3 per cent jaundice following fresh blood transfusion. Belk, Henry, and Rosenstein (30), however, find no greater increase in jaundice when stored blood is used instead of fresh blood.

Our results show a definite relationship between the age of the blood and the rise in the icterus index. Whereas the fresher blood produced almost no increase in the index, blood older than five days showed a tendency to produce a progressively greater rise as it aged. The parallelism between the curve of the icterus index rise and that of the fragility of the

red blood cells in stored blood is quite striking (fig. 2). The obvious conclusion is that, as the blood ages, the older red cells, being more fragile, are disintegrated to a greater degree in the recipient following transfusion, liberating free hemoglobin and giving rise to icterus. This phenomenon is discussed more fully later.

Analysis of reactions. The cause of transfusion reactions remains obscure. Lewisohn and Rosenthal (24) showed that proper cleansing of apparatus was most important in reducing the number of reactions to a minimum. However, in spite of this attempt by us to clarify the situation there was still an incidence of chills of 1 to 2 per cent and a total of all reactions of 13.8 per cent at this hospital before the institution of the blood bank. Some investigators insisted that reactions were due mostly to minor blood group incompatibilities involving the M and N and A_1 and A_2 factors. We have on hand much unpublished data to show that these factors are of little consequence and rarely, if ever, are the cause of reactions, minor or major.

The use of universal donors whose serum contains high titre agglutinins is also not important in the causation of transfusion reactions, as shown by Rosenthal and Vogel (56). Not only is the dilution of the serum in the recipient's blood stream sufficient to obviate this factor, but in addition Levinson and Cronheim (31) have shown that the serum and tissues of the recipient contain adequate neutralizing power for these transfused isoagglutinins.

The RH agglutinin of Landsteiner and Weiner (57) has recently been found to be a most important factor as a cause of transfusion reactions in patients receiving repeated transfusions. RH negative recipients when transfused repeatedly with RH positive blood may become sensitized by the antigen and develop anti-RH agglutinins (58). Similarly Levine and Stetson (59) have shown that sensitization of an RH negative mother may occur by means of an RH positive fetus. One of us (P. V.) has had a number of cases in which RH agglutinins present in the serum of the recipients was responsible for hemolytic transfusion reactions. With the use of blood from RH negative donors no further reactions occurred in these patients.

According to Bender (32) hemolysis of the red blood cells releases a substance capable of causing constriction of the iris of a cat's denervated eye. Further investigations of this parasympathomimetic substance by Bender and Wachtel (33) have proved it to be a lecithin-like compound. The type of transfusion reaction may depend therefore to a large extent upon the amount of lecithin-like substance liberated from the hemolyzed cells.

Reports of reactions following the use of stored blood for transfusions indicate an incidence which varies from 1 or 2 per cent to as much as 50 per cent, depending upon the observer. Most American workers, however, have found a more or less uniform percentage of reaction varying

from 5 to 10 per cent. Thus Diggs and Keith (34) reported a total reaction percentage of 6.7. DeGowin and Hardin (35) found not more than about 3 per cent, with 1.4 per cent of chills. Belk, Henry, and Rosenstein (30) reported jaundice or hemoglobinuria in seven of 400 "bank" transfusions and an incidence of all other reactions of 10.0 per cent.

During the first two year period of operation of the blood bank, a total of 4,034 transfusions were given, 46 per cent Group O, 37 per cent Group A, 13 per cent Group B, and 4 per cent Group AB. For the six month period immediately preceding the institution of the blood bank, a study of 1,000 fresh citrated blood transfusions showed reactions totaling 13.9 per cent of which 2.5 per cent were chills. Similarly, 1,000 cases analyzed immediately following the establishment of the blood bank showed an almost equivalent number of reactions totaling 13.4 per cent of which 2.4 per cent were chills. The type of reaction varied somewhat, however (see table 3), jaundice following 1.6 per cent of the stored blood transfusions and absent

TABLE 3

Comparison of incidence of reactions following transfusions of bank blood and of fresh citrated blood

	TEMPERATURE RISES			URTICARIA	CHILLS	JAUNDICE	TOTAL
	1-2°	2-3°	Over 3°				
Percentage reactions (blood bank) (1000 cases).....	3.0	3.1	1.4	1.8	2.5	1.6	13.4
Percentage reactions (indirect citrate) for six month period prior to inception of blood bank (1000 cases).....	5.5	3.0	2.8	0.2	2.4	—	13.9

following fresh transfusions. The incidence of chills was approximately the same (2.5 per cent). Subsequent analysis revealed that as the age of the blood increased there was an apparent increase in percentage and types of reaction. Although Figure 3 cannot be considered a true graphic representation because of the small number of transfusions given of blood stored for longer periods, there is a significant increase in the percentage of reactions (table 4, and fig. 3). As the blood ages there is an apparent increase in all types of reaction. Because of this increase in undesirable response, the age of blood dispensed was limited to ten days. With this change of procedure a sharp drop in reactions occurred so that our total percentage now has dropped from 14.7 per cent to an average of 5.7 per cent per month. The total number of reactions of all types was 381 or an average of 9.4 per cent. Semi-annual averages of all transfusion reactions have shown a steady decrease. For the first six month period there was an average of 14.6 reactions, for the second six month period, 11.1 per cent, for the

third six month period, 7.4 per cent, and for the fourth six month period, 5.7 per cent.

The number of cases of jaundice has decreased markedly. This jaundice was apparently due to the liberation of hemoglobin from the older, more fragile, red blood cells which disintegrated within the blood stream of the recipient. Most instances of jaundice occurred in postoperative cases. The slight depression in liver function following anesthesia was

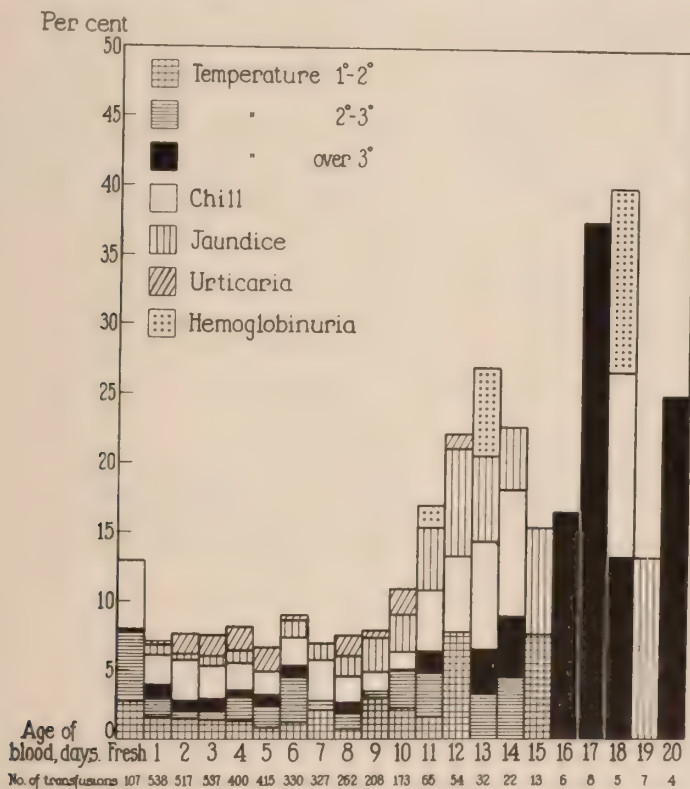


FIG. 3. Percentage and type of reaction following transfusion of blood stored from 1 to 20 days.

presumably sufficient to permit the rapid, though transient, accumulation of bilirubin in the blood stream producing jaundice.

It is obvious that familiarity with the procedure and limitation of the age of blood dispensed to 10 days have been important factors in reducing the percentage of reactions to about one-third of the original level.

MORPHOLOGICAL CHANGES

Method of study. Blood collected from thirty-one donors was reserved for experimental purposes. All specimens were collected in the routine manner in Mason jars to which had been added sufficient sodium citrate

to make the final dilution 0.38 per cent. After thorough mixing samples were removed from each jar immediately after collection, and placed in 100 cc. Erlenmeyer flasks. These were examined at regular intervals along with other samples removed from the original Mason jar at the same time for comparison. Slight variations between the two samples did occur but were within the experimental error. Although Depp (36) and others assert that shaking of the flasks causes an increase in hemolysis, we have been unable to find any important difference between specimens removed before and after slight shaking. Rous and Turner (37) and DeGowin, Harris, and Plass (38) have reported findings similar to ours.

Fragility. Blood samples to be tested were washed with 0.89 per cent saline until the supernatant plasma was clear. Three washings were usually sufficient. 0.1 cc. of a 20 per cent suspension of cells was then added to 2 cc. of hypotonic saline in dilutions ranging from 0.24 to 0.72

TABLE 5
Changes in hemogram in blood stored 1-11 days

	DAYS					
	1	3	5	7	9	11
Hemoglobin in per cent (Sahli)....	90	90	90	90	90	90
Red blood cells in millions per cu.mm.....	4.65	4.50	4.25	4.10	3.95	3.86
White blood cells per cu.mm.....	6000	2100	2000	2000	1950	1900
Platelets in thousands per cu.mm..	170	120	80	70	50	40
Total neutrophiles.....	(3600)	(1764)	(105)	(40)	(19.5)	
Neutrophiles, percentage of white blood cells.....	60	42	5	2	1	1
Lymphocytes, percentage of white blood cells.....	30	50	95	98	98	98
Fragility to hypotonic saline.....	0.44	0.48	0.56	0.68	0.72	0.72

per cent and, after mild agitation to insure thorough mixing, the contents of the tubes were centrifuged at a low speed. The occurrence and degree of hemolysis were noted.

An increased susceptibility to hemolysis was evident by the third day and advanced rapidly, so that by the tenth day even normal saline caused marked laking of cells (table 5 and fig. 2). Rous and Turner (37); Scudder, Drew, Corcoran, and Bull (39); Kolmer (40); Gwynn and Alsever on placental blood (41); Belk, Henry, and Rosenstein (30); and Depp (36) have reported similar results.

The increased hemolysis is apparently related to a disturbance of the electrolyte balance between cell and plasma. Rous and Turner demonstrated that the rate of hemolysis is increased by the addition of electrolytes to the blood. Although no definite changes in the stroma of the red blood cells have been described, physico-chemical changes in the cell mem-

brane undoubtedly occur with a resultant increased fragility of the cells in hypotonic saline.

Rous and Turner showed that the addition of glucose to blood rendered incoagulable by sodium citrate decreased the rate of hemolysis. Robertson (11), employing this method of preservation, found it necessary first to remove the supernatant plasma before using the blood because of its large volume and high concentration of sodium citrate. Depp (36) and Duran, Aleu, and Sardá (42) found that a glucose-citrate solution preserved cell elements longer and DeGowin, Harris, and Plass (38) have indicated that a modified Rous-Turner solution is most efficacious in reducing the rate of hemolysis.

Investigations following the use of IHT solution have given conflicting results. Bagdassarov (43) and Vaughan (19) have found that with the use of IHT solution there was a decrease in the rate of hemolysis. However, Lindenbaum and Stroikova (44), as well as many American observers, found that the solution of the Moscow Institute of Hematology gave no better results than sodium citrate and was not as good as glucose-citrate.

For the past few months we have been employing DeGowin's glucose-citrate mixture in a few blood specimens and our findings are similar to his. The rate of hemolysis is diminished but changes in the platelets and white cells continue as in the case of sodium citrate without glucose.

After 5 to 10 days of storage, citrated blood kept at 2 to 4°C. shows a diffusion of hemoglobin pigment into the supernatant plasma. The effect of this free hemoglobin on the patient is of little or no significance. Ottenberg and Fox (45) showed that a considerable amount of hemoglobin (72 mg. per kg. of body weight in women and 92 mg. per kg. body weight in men) must be present in the blood stream before the renal threshold is exceeded with subsequent appearance of free hemoglobin in the urine. Thus hemoglobinuria occurs rarely and only when accompanied by a severe chill, rise in temperature, and marked intravascular hemolysis.

Hemoglobin, red blood cells, white blood cells, platelets, and differential counts. Hemoglobin values, as determined by the Sahli method and oxygen capacity of the blood (Van Slyke), remained unchanged (fig. 5). Reports from other laboratories have been confirmatory. The erythrocytes, however, began to hemolyze soon after withdrawal from the donor and this hemolysis continued at a slow rate as long as observed. After 10 days the red blood cells had decreased almost one million per cubic millimeter. The decrease in red cells coincides with the increase in fragility of the erythrocytes (table 5, and figs. 2 and 4). Smears were made at daily intervals and the red and white blood cells examined. Although measurements of cell diameters were not made, the red cells appeared larger and an increasing number of "ghost forms" were present after the third day.

The leucocytes followed a fairly typical course. Within 3 days the

leucocyte count had dropped to an average of 2,100. This initial rapid decrease in total white cells is due to a disappearance of polymorphonuclear neutrophils from the blood. The average total polymorphonuclear count decreased from 3,600 per cubic millimeter to approximately 20 per cubic

Average Change of Hemogram in Stored Blood

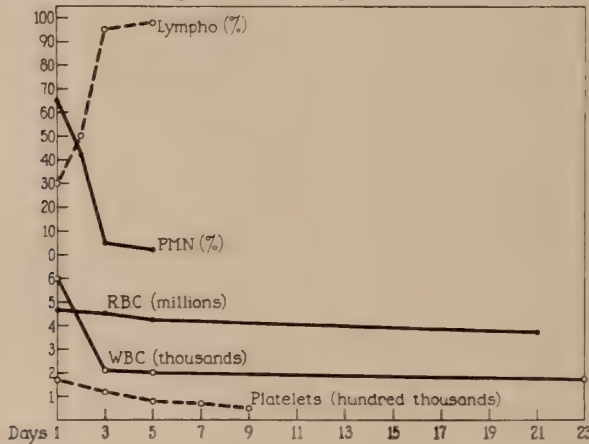


FIG. 4. Changes in hemogram in blood stored 1 to 11 days

Three Typical Curves Showing Changes of Glucose, Lactic Acid, pH and Oxygen Carrying Capacity

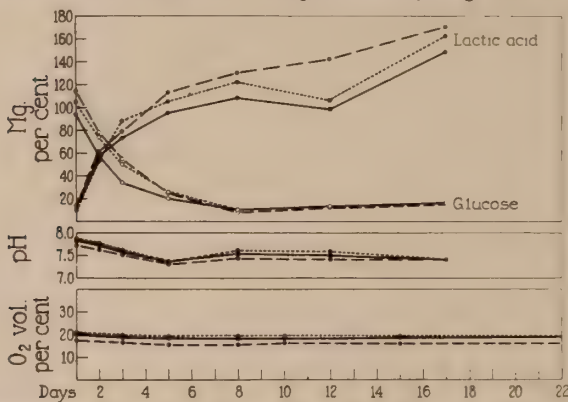


FIG. 5. Three typical curves showing changes in glucose, lactic acid, pH, and oxygen-carrying capacity in blood stored 1 to 22 days.

millimeter within 10 days (table 5, and fig. 4). Significant degenerative changes were observed morphologically in the neutrophils, which may be correlated with the decrease in opsonic index found by Kolmer (40). The nuclei of the cells became pycnotic and shrunken. The cytoplasm became vacuolated and disintegrated, leaving naked, shrunken nuclei as the last

remnant of the cell structure. The eosinophiles and basophiles degenerated more slowly, at a rate approximately equal to that of the lymphocytes. These cells also showed similar degenerative changes as the time of storage increased.

Soon after withdrawal of the blood the platelets began to clump and disintegrate. At the end of 5 days only 50 per cent remained intact, and at the end of 10 days less than one-third could be counted. If the small fibrin clots occurring in any blood collected with an anti-coagulant are examined, many clumped platelets will be found enmeshed in the fibrin.

Results similar to the above have been obtained by Bagdassarov (43); Drew, Edsall, and Scudder (46); Belk, Henry, and Rosenstein (30); Kolmer (40).

Chemical studies. Determinations of lactic acid, glucose, pH, and oxygen capacity were made on three specimens of blood at regular intervals. Figure 5 illustrates the typical changes encountered.

Lactic acid determinations were made according to the gasometric method of Avery and Hastings (47), glucose determinations according to the Folin-Wu method (48), and pH determinations by means of the glass electrode. The oxygen-carrying capacity was determined by the Van Slyke and Neill method (49).

Blood sugar levels were determined immediately after withdrawal and at regular intervals. It was found that no significant decrease occurred if sodium fluoride in sufficient concentration was added and the blood examined within 24 hours. Determinations on blood drawn occasionally late at night and rendered incoagulable with fluoride could thus be made the following day. Subsequent determinations were made on citrated blood. (Samples of blood were collected in separate 30 cc. test tubes and examined at regular daily intervals.)

The glucose disappeared rapidly from the stored blood. Within 48 hours the blood sugar had dropped from an initial level of 95 to 115 mg. per cent to between 30 and 55 mg. per cent. The fall continued until the eighth day, when further determinations were too low to be recorded accurately.

With the glycolysis a sharp rise in lactic acid occurred. The initial level of about 10 mg. per cent was found to be 50 to 60 mg. per cent in 24 hours and the rise continued until at the end of 17 days the lactic acid was found to vary between 148 to 170 mg. per cent.

The buffering ability of the blood remained fairly uniform, however, and pH levels varied between 7.8 and 7.4. The citrate used had a pH of 7.83 and at the end of 2 weeks was more or less unchanged.

Prothrombin. Reports on prothrombin changes in stored blood have been variable. Rhoads and Panzer (50) were the first to demonstrate a depletion in the prothrombin content of stored blood. They found a 40 per cent drop within 3 days of storage and a progressive decline thereafter.

They concluded that blood stored longer than 3 days was of slight therapeutic value in cases of jaundice with a prothrombin deficiency. Quick (51) supported the above view and advised the use of fresh blood in cases of jaundice with bleeding. DeGowin, Harris, and Plass (52) showed that the prothrombin disintegrated slowly, remaining at about 50 per cent of the normal level at the end of twenty days. Ziegler, Osterberg, and Hovig (53) found that the plasma prothrombin diminished slowly, so that by the thirty-sixth day 40 per cent of the total still remained. Lord and Pastore (54) found that blood stored nine days contained 75 per cent of the total prothrombin and felt that it was an adequate source of prothrombin. Rheinhold, Valentine, and Ferguson (55) reported a drop to 73 per cent of the normal prothrombin in blood stored three days, and to 55 per cent in six to seven days, but felt that their results on blood used within three days were good. The results of our own prothrombin studies are in accord with the more favorable reports.

Specimens from three donors were obtained under sterile conditions at each phlebotomy session and kept in the blood refrigerator at a temperature of 2 to 4°C. Thirty specimens of blood were obtained in this fashion over a period of 21 days. At the end of this period, three specimens each of fresh, 3, 5, 7, 9, 12, 14, 16, 19, and 21-day-old blood were available. Quick's method was followed in every respect, except that citrated plasma was used instead of oxalated plasma.

The same thromboplastin was used throughout the series. The only possible variation was in the individual bloods. To overcome this, an average prothrombin time was determined from the three different bloods of each age period. It was found that individual variations were almost negligible. From each average prothrombin time the prothrombin index and the prothrombin concentration in the plasma were obtained.

In order to determine whether there was any difference in prothrombin concentration in citrated blood fresh citrated blood was diluted with varying portions of the same plasma in which the prothrombin had been previously inactivated by heating and compared with oxalated blood. The results obtained paralleled closely those obtained by Quick with oxalated plasma. The prothrombin index is obtained by the following equation:

$$\text{P.I.} = \frac{\text{control (seconds)}}{\text{unknown (seconds)}} \times 100.$$

These studies reveal that a deficiency in prothrombin does occur but that it is not evident until the seventh day. If these findings represent the effectiveness of stored blood in improving coagulation, then one may assume that through the first five days stored blood is as beneficial as fresh. On the seventh day the concentration was found to be only 60 per cent of normal. There is a progressive drop from then on (fig. 6).

Inasmuch as a prothrombin deficiency is so frequently the only important

variation from normal in the laboratory findings in jaundiced patients, aside from the jaundice itself, it seems wise at this time to use bloods less than a week old in such cases.

Antibody content. Transfusions have been employed to a great extent as a supportive measure in severe infections. There is no doubt that the beneficial action of transfused blood is dependent not only on the correction of anemia, if present, but also on the bactericidal and bacteriostatic action of the serum. The phagocytic activity of the white cells is relatively unimportant because of the small number introduced during the course of a transfusion. Kolmer has shown that serum complement in the presence of citrate is preserved in an unchanged state for two to three weeks.

Average Changes of Prothrombin in Stored Blood

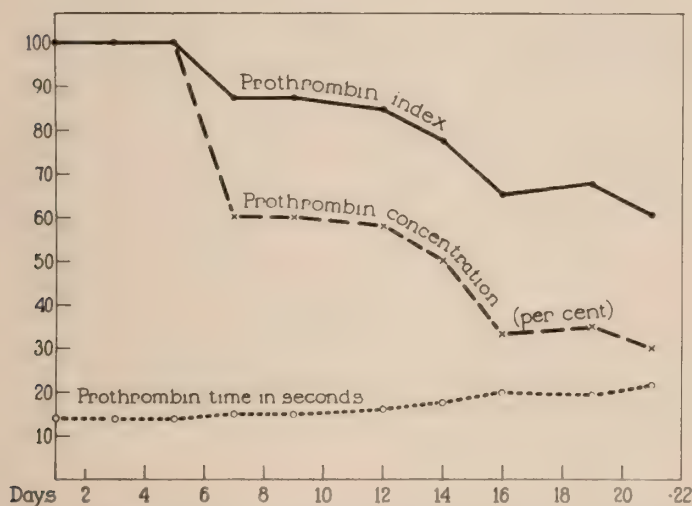


FIG. 6. Average change in prothrombin in blood stored 1 to 21 days

The protein pattern of stored blood or serum remains unchanged for months. Since antibodies are associated with the globulin fraction, it was felt that these too should show no change. Our results, compiled with the assistance of Mr. Charles Greenwald of the New York City Department of Health, confirmed this view.

Twelve specimens of bank blood were tested for diphtheria antitoxin content by combining 1 cc. of plasma with varying minimum lethal doses of diphtheria toxin and injecting the mixture into guinea pigs. Four of these specimens did not protect against one minimum lethal dose of toxin, three specimens protected against 2 to 3 minimum lethal doses of toxin, and two specimens protected against 6 to 8 minimum lethal doses of toxin.

For the first four months there was no noticeable diminution of potency

in any of the specimens. By this time all the specimens were hemolyzed. After the fifth month, the specimen that neutralized 6 minimum lethal doses of toxin showed a loss of about 15 per cent of its neutralizing value. Since no decrease occurred in the antibody tested, it was assumed that other circulating antibodies acted similarly. It was concluded, therefore, that the antibodies found in circulating blood show no significant change and are active in protecting against their specific antigens.

Urobilinogen elimination. An increase in hemolysis in the blood stream is always accompanied by an increase in the urobilinogen content of the urine and stool. A fairly accurate method is thus available for measuring the length of survival in the recipient of transfused blood since rapid destruction of the transfused red blood cells would be accompanied by a correspondingly rapid conversion of the free hemoglobin to bilirubin and urobilinogen. Quantitative studies were undertaken with Watson's modification of Terwen's method. Three patients suffering from aplastic anemia were treated with transfusions of blood of varying ages. Fresh blood caused no increase in urobilinogen content of the urine and stool during a period of 1 week following the transfusions. As the age of the blood increased, an increase in pigment excretion occurred that was directly proportional to the age of the blood. The increase was rapid, occurring within 24 to 48 hours, and assumed large proportions in blood more than two weeks old. Our results thus show that freshly transfused red blood cells have a longer life in the recipient than those of stored blood.

SUMMARY

A review of the results of two years' experience with a blood bank indicates that it is an important and integral part of a hospital. It has solved not only a financial problem but has made transfusions available in unlimited numbers to ward patients.

Simple procedures in collecting, storing, and dispensing blood have proved of greatest value. The open-system has been found most adequate and in not a single instance has there been any evidence of bacterial contamination of blood kept at 2 to 4°C. over a period of weeks. The intravenous drip method, previously suggested, is another simple procedure which has been followed by good results.

The Kahn reaction on the donor's blood, as well as compatibility tests between the donor's and the patient's blood, are imperative. There has not been a single case of transmitted lues over this two year period; furthermore, no other serious effects from any transfusion from the blood bank have occurred.

Chemical and morphological changes take place in stored blood, but these are not of such consequence that they contraindicate its use in transfusion, especially in respect to its most important indications, shock and hemorrhage. In non-surgical conditions, in which the question of the red

blood cell count is of consequence, it must be conceded that fresh blood is more desirable. This is brought out by experimental studies on the comparative effects of fresh and stored blood on the hemoglobin, icterus index, and urobilinogen excretion of the recipient. The results indicate that stored red blood cells are more rapidly eliminated from the blood stream than fresh red blood cells. Coagulation factors of the plasma, especially prothrombin, and bactericidal factors, remain fairly potent during the first seven days of storage. It should be emphasized, however, that blood stored up to ten days is still very useful in blood transfusion. After the ten day period, it need not be entirely discarded since the plasma can be removed and made available for use in cases of shock, hemorrhage, and nephrosis.

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CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Wednesday, November 29, 1939

Multiple Myeloma with Cord Involvement

[From the Neurosurgical Service of Dr. Ira Cohen]

History (Adm. 444777; P.M. 11289). A fifty-six year old white man entered the hospital for the first time on August 21, 1939. He had pneumonia with pleurisy four months before admission. Shortly after this illness he noted low back pain which radiated down the back of his left leg. For the last seven weeks prior to admission this pain had steadily increased in intensity, was aggravated by flexion of the back, and was associated with weakness of the lower extremities. For the last ten days he had urinary retention, dribbling, and inability to control the anal sphincter. The illness caused a weight loss of twenty pounds.

Examination. The patient was a chronically ill man. The urinary bladder was distended. The sacro-iliac joints were tender to percussion. The Lasègue sign was bilaterally positive. The anal sphincter was lax and easily admitted three fingers. There was wasting of the muscles of both legs, with weakness, diminished knee jerks and absent ankle jerks. There was hyperesthesia over the distribution of the left sacral fourth and fifth nerves. The clinical impression was a spinal cord tumor of undetermined type.

Laboratory data. The hemoglobin was 68 per cent (Sahli); white blood cells, 14,800 with 62 per cent polymorphonuclear leucocytes. The blood chemistry findings were normal. The urine concentrated as high as 1.020, contained a trace of albumin, occasional red blood cells and white blood cells, and on culture *B. coli* and enterococcus were demonstrated. X-ray studies of the bladder revealed several large diverticulae. X-ray examination of the spine and sacrum showed hypertrophic spondylitis.

Course. A residual urine of 18 ounces was found. Cystoscopy revealed edema of the floor of the bladder involving the sphincter. Several diverticulae were visualized. A bilateral vas ligation was then performed. Simultaneous pressure studies of the cerebrospinal fluid from the first and fifth lumbar vertebrae were done. There were no significant findings. The Pandy test, however, was 4 plus. Shortly after the vas ligation, the patient's condition became poor. He had fever for a prolonged period and a urinary infection was suspected. During this episode he had a 300 cc. hemorrhage of bright red blood from his bowel. The exact source of this bleeding was not determined. Lipiodol studies of the spinal cord were then done. A filling defect suggesting a neoplasm was demonstrated in the extreme lowermost portion of the spinal cord. An exploratory laminectomy from the fourth lumbar vertebra to the second sacral was performed and an extremely large, malignant-looking, extra-dural tumor was found. This was inoperable and a biopsy was taken. The patient left the table in poor condition and died in a few hours despite supportive therapy.

Necropsy findings. Dr. Klemperer. The lower lumbar vertebrae and sacrum were largely invaded and destroyed by multiple myeloma. The tumor almost completely filled the presacral area, and the cauda equinus was imbedded within it. Multiple myeloma were also found in the ribs and ilium. The other organs were negative.

Comment. Dr. Bachr: I would like to ask our roentgenologist, Dr. Sussman, why this lesion was not demonstrable roentgenographically. I realize that the recognition and differential diagnosis of destructive bone lesions is difficult.

Dr. Sussman: This was a definite error of interpretation. Large clear areas were seen in the sacrum. They were interpreted as gas bubbles in the intestine. However, we now know that these clear areas were due to sacral destruction. The lesions in the iliac bone were not revealed by x-ray examination. The x-ray studies were repeated after the death of the patient, with similar negative results.

Dr. Wechsler: Urinary difficulty may occur early in spinal cord lesions. Rectal incontinence is usually evidence of an advanced lesion.

Dr. Bachr: Backache is often the first symptom of multiple myeloma. The diagnosis of this disease can be made by aspirating and examining the sternal bone marrow. This should be done in every case of obscure bone marrow neoplasm. If it had been done in this instance, a needless exploratory laminectomy would have been avoided.

Reported by Abner Kurtin, M.D.

Syphilitic Heart Disease

[From the Medical Service of Dr. B. S. Oppenheimer]

History (Adm. 447269; P.M. 11296). This was the first admission of a forty-five year old Italian man whose illness began seven weeks before admission with shortness of breath on moderate exertion. At about the same time he began to experience upper abdominal cramps, usually postprandial. Orthopnea required two pillows. One week before admission he observed that his ankles had become swollen. For six days he had experienced recurring attacks of nocturnal dyspnea. He began to cough and had been expectorating three ounces of frothy, frankly bloody sputum daily for four days. There was no history of precordial pain, antecedent hypertension, rheumatic fever, respiratory infection, or venereal disease.

Examination. The patient was an acutely ill, cyanotic, orthopneic, dyspneic, middle aged man, who coughed up bloody sputum. His pupils were irregular, the right did not react to light, the left reacted only sluggishly; both reacted well in accommodation. The sclerae were subicteric. The trachea was in the midline; there was no tracheal tug. The neck veins were engorged, almost to the bursting point on the right side. Retromanubrial dullness was normal. There was slight dullness at the right lower lobe with occasional moist sticky rales. In the left axilla there was a pleural friction rub. The apex beat of the heart was in the seventh space, 14 cm. from the mid-sternal line. The heart sounds were barely perceptible. No murmurs were

audible. The rhythm was punctuated with numerous extrasystoles. P2 was louder than A2. The left radial pulse was definitely stronger than that on the right; the latter was barely perceptible. The blood pressure on the right was 90 systolic and 80 diastolic, and in the left upper extremity it was 130 systolic and 80 diastolic. The abdomen was slightly distended; the liver was enlarged four fingers below the costal margin. There was pitting edema of the legs and thighs, extending up the mid-abdomen. The deep reflexes were equal, but slightly depressed. The patient was euphoric. The clinical impression was luetic heart disease.

Laboratory data. The blood urea nitrogen was 52 mg. per cent; sugar, 105 mg. per cent; total protein, 5.5 per cent. The icteric index was 9. The blood Wassermann reaction was positive, 1 plus. Venous pressure was 22 cm. on each side with a rise to the top of the tube on right upper quadrant pressure. Saccharine circulation time was 45 seconds. Sedimentation time was over 2 hours. Bedside x-ray examination showed a clouding at the base of the right lower lobe; the left ventricle was markedly enlarged in the region of the apex. The electrocardiogram showed regular sinus rhythm, left axis deviation, QRS of high voltage, slurred and measuring 0.14 second. The RT was slightly depressed in lead I, and elevated in lead III.

Course. The patient presented a picture of severe, universal heart failure. He continued to expectorate large quantities of frankly bloody sputum. However, despite the obvious seriousness of his condition, he remained cheerful throughout his course. He was given esidrone and ammonium chloride in an attempt to improve the congestive heart failure by diuresis, but he failed to respond and died on the third hospital day.

Necropsy findings. The *aorta* presented a classical picture of syphilitic mesoarteritis, with its characteristic wrinkling. The process was very extensive and involved not only the ascending aorta and arch, but also the thoracic and abdominal aorta. There had resulted a complete stenosis of the left coronary ostium, as well as a very marked narrowing of the origin of the innominate artery, and moderate narrowing of the orifice of the left carotid artery. The left coronary artery itself was patent and relatively normal throughout. The left *heart* was strikingly dilated, almost globular in outline. This was the result of two factors, namely aortic insufficiency with regurgitation, and of even greater importance the marked thinning of the myocardium due to severe fibrosis. The *lungs* showed an enormous infarction of the entire right lower lobe. This was due to an embolus originating in thrombi of the peri-prostatic venous plexus. There was a necrotizing mucosal lesion in the intestine.

Comment. *Dr. Klemperer:* This case illustrates the well known fact that in luetic aortitis there can be a complete closure of a coronary ostium with secondary fibrotic changes in the myocardium even though the rest of the coronary artery is perfectly normal. The intestinal mucosal lesions are in all probability a result of the terminal state of shock, as has been recently shown by Penner and Bernheim.

Dr. Baehr: Although there was considerable ante-mortem clinical discussion concerning the cause of this man's illness, the majority opinion was in favor of luetic heart disease. The diagnosis should have been made with definiteness in view of the sudden onset of heart failure, its very rapid progression, the lack of response to therapy, the pupillary findings, the positive Wassermann reaction and the unequal pulses and blood pressure. Luetic aortitis may be unrecognized until one of two things occur. The

patient may suddenly drop dead due to claudication of the coronary arteries; this is a very common cause of sudden death. Secondly, the patient may rapidly develop heart failure due to insufficiency in coronary blood flow through the narrowed ostia. Once this sets in it is usually steadily and rapidly progressive. The reduced coronary blood flow through the narrow ostia is still further lessened with the onset of heart failure. This results in myocardial damage of universal distribution and of right and left heart failure. The lack of response to therapy is due to the vicious cycle, reduced blood flow through the narrowed ostia, still further reduced by heart failure. Although the clinical features of luetic aortitis can exactly simulate an acute coronary thrombosis even to the production of myomalacia, actual sclerosis and thrombosis of the coronary artery due to lues is rare. The narrow ostia due to syphilitic aortitis and the resulting reduction in coronary flow and coronary blood pressure seems to protect the coronary arteries from arteriosclerosis. Behind the narrowed ostia they are usually found almost free of arteriosclerotic changes.

Dr. Hiltzig: The marked venous engorgement limited to the right side of the neck was a misleading point until it was shown that the cause did not lie in an unequal venous pressure but rather, resulted from an absence of the left external jugular vein. Careful examination revealed that the smaller neck veins on this side were also distended and tense.

Reported by *Maz Ellenberg, M.D.*

Carcinoma Developing in a Bladder Diverticulum

[From the Surgical Service of Dr. A. Hyman]

History (Adm. 443343; P.M. 11219). This sixty-four year old white man entered the hospital for the first time on November 17, 1937 because of urinary difficulties. Ten years before admission he developed increased frequency of urination, dysuria, and pyuria. A suprapubic cystotomy was performed and four vesical calculi were removed. At that time he also noted a reducible rectal prolapse. Four years previously there was a recurrence of pyuria, nocturia 2 to 3 times, and burning on urination which persisted. Two months prior to admission hematuria was noted. There had been no chills or fever, no constipation. His general health, otherwise, had remained good.

Examination. He was a well developed man who had poor color. The heart was not enlarged, the rhythm was regular, no murmurs were heard. The blood pressure was 136 systolic and 76 diastolic. The lungs were normal except for a few râles at both bases. The lower abdomen was distended and tympanitic. A suprapubic sear was present. A one and a half inch rectal mucosal prolapse was present. Rectal examination showed the prostate to be smooth, firm, regular, and not enlarged. A neurological examination was negative.

Laboratory data. Urine: Alkaline reaction; specific gravity, 1.022; trace of albumin, and microscopically showed many clumps of white and some red blood cells.

Blood: Hemoglobin, 86 per cent; red blood count, 4,570,000; white blood count, 6,500 with a normal differential; blood urea nitrogen, 19 mg. per cent; blood Wassermann reaction, negative. Excretory urogram showed a normal upper urinary tract, a small trabeculated bladder and a large diverticulum of the bladder, as well as evidence of an enlarged prostate. Retrograde cystogram showed a large right anterior diverticulum measuring approximately 7 cm. in diameter.

Course. Attempts at decompression of the distended bladder were unsuccessful until a silk Conde catheter was used. A total of 28 ounces of foul smelling, thick urine was then removed. A catheter was left indwelling and the urine gradually cleared considerably. Cystoscopy and bilateral vasectomy were then performed. The cystoscopic examination showed a diffusely inflamed bladder mucosa. The prostate was only moderately enlarged. In view of the fact that both a diverticulectomy as well as a prostatectomy would be necessary, and that the patient's general condition was poor, it was felt that it was inadvisable to carry out these procedures. However, because the patient was more disturbed by his rectal prolapse, an excision was performed. The postoperative course was uneventful. He left the hospital on December 14, 1937, ten days after operation feeling improved, voiding spontaneously, but he still had 12 ounces of residual urine.

Second admission. The patient was re-admitted one week later on December 22, because of the development of fever up to 101°F., general weakness and suprapubic tenderness. A few râles were heard at both bases. The blood pressure was 110 systolic and 70 diastolic. The blood urea nitrogen was 20 mg. per cent. The blood count was essentially unchanged. The urine showed a trace of albumin, a moderate number of clumped white blood cells and a few red blood cells. An indwelling catheter was inserted on admission. Three days later he developed substernal pain radiating to the left axilla associated with vomiting and weakness. He became pale; the pulse was slow, rate 50 to 60 per minute; the temperature was 97°F. Cheyne-Stokes respirations were present. The blood pressure was 116 systolic and 50 diastolic; the heart sounds were distant. An electrocardiogram was negative. The following day a pleural friction rub was heard in the left chest posteriorly. The episode was then attributed to a pulmonary infarction. He improved rapidly. Nevertheless, his condition did not warrant any radical surgery. He was taught to catheterize himself. He was discharged on January 8, 1938 after two weeks, afebrile.

Third admission. Following discharge he was treated with bladder irrigations and urinary antiseptics. Under this regime the pyuria improved considerably and the residual urine which had been 12 ounces, fell to 6 ounces. Ten days prior to this admission he began to have severe pain on urination. The urine grossly contained pus and mucus. The temperature rose as high as 103°F. Because of this and the development of extreme tenderness in the left costovertebral angle, he was returned to the hospital on May 6, 1938 with a diagnosis of left pyelonephritis. In the hospital, in addition to the costovertebral findings he had diffuse abdominal distention, and marked tenderness in both lower quadrants. Numerous crepitant and moist râles were heard over both lower lobes.

The hemoglobin was now 105 per cent; red blood count, 6,090,000; white blood count, 10,850 with 82 per cent polymorphonuclear leucocytes; blood urea nitrogen was 15 mg. per cent. The urine was loaded with clumped white blood cells. He developed transient signs of fluid in the left chest and on one occasion a friction rub was heard over the left lower lobe. A cough was present and he had hemoptysis once. His course was marked by fever up to 103°F. at first but this gradually subsided to a normal level, coincidental with the administration of sulfanilamide. He was discharged six weeks after admission, after he had refused suprapubic cystotomy.

Fourth admission. Since his last admission he had developed fever, lower abdominal tenderness and foul cloudy purulent urine. The residual urine on July 11

was 20 ounces. He finally consented to a suprapubic cystotomy which was performed. A diverticulectomy was considered too hazardous a procedure for him. Recovery was uneventful. At the time of discharge on July 30, 1938 he was afebrile.

Final admission. At the time of this admission on July 17, 1939 he was completely uncooperative, drowsy and no satisfactory history could be elicited. Apparently the purulent suprapubic drainage had persisted and his general condition had become progressively worse. He appeared malnourished, and complained of severe suprapubic pain. The heart sounds were of poor quality; a systolic murmur was heard at the apex; the heart rate was slow but totally irregular. The suprapubic drain was present *in situ* and drained foul, purulent urine. The hemoglobin was 100 per cent; blood urea nitrogen, 20 mg. per cent; sugar, 90 mg. per cent; chlorides, 515. Urine culture showed a *B. proteus* and an enterococcus. Flat plate of the abdomen showed no evidence of calculi. An electrocardiogram showed auricular fibrillation. The course was rapidly down hill. The suprapubic drainage became markedly bloody. The patient became comatose. His blood urea nitrogen rose to 41, the chlorides to 655, and the carbon dioxide combining power was 44.2 volumes per cent. His temperature hovered around 100°F. He ceased one week later.

Necropsy findings. *Dr. Klemperer:* The bladder showed typical changes of prolonged obstruction. On the right side posteriorly there was a diverticulum 2 inches deep. At the base of this diverticulum there was a mushroom-like growth (microscopically squamous cell carcinoma) which invaded the surrounding tissue. There was no evidence of metastases. The ostium of the right *ureter* was compressed by this growth, and the *kidney* on that side was hydronephrotic, and was involved in a severe pyelonephritis. On gross examination the *heart* showed a few areas of fibrosis. Microscopically, however, these were areas of homogeneous appearance which by special stains were shown to be amyloid. There were no amyloid changes elsewhere in the body. Instances in which amyloid is deposited in organs usually not involved and absent in the usual sites, such as liver, spleen and kidneys have been designated "paraamyloidosis." As a rule such amyloid deposits do not give the usual staining reactions. Atypical amyloid disease usually occurs in the absence of the known causes for this disease. The carcinoma of the bladder may be regarded as adequate explanation in this case because malignant tumors are known to be associated with amyloidosis.

Comment. *Dr. Bachr:* The comatose state into which this patient eventually subsided was due to a combination of infection and renal insufficiency.

Dr. Hyman: Carcinoma arising in a bladder diverticulum is rare. I can recall but three cases during my entire experience in this hospital. For purposes of classification we must differentiate between carcinoma arising in a diverticulum, and tumor arising outside the diverticulum and invading it secondarily. If the carcinoma is large enough it can be demonstrated by cystoscopy or contrast x-ray. The finding of *Bacillus proteus* is of interest. In the past two years the incidence of such infection has risen markedly. Other clinics have had similar experience. The organism is extremely resistant to therapy. Occasionally massive doses of sulfanilamide may clear the urine.

Reported by Abner Kurtin, M.D.

CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D., *presiding*

Monday, February 10, 1941

Case 1. Amyotrophic Lateral Sclerosis

[From the Neurological Service of Dr. I. S. Wechsler]

History (Adm. 455549; P.M. 11510). A man, aged 49, entered this hospital on April 23, 1940. Eleven months earlier he noted for the first time twitching and weakness of the right hand. Gradually, the right arm became similarly affected and somewhat later the left arm and leg became involved. The limbs became stiff and the fingers of the right hand were clenched, but could still be extended passively. His gait became shuffling and he would occasionally fall to the ground. In the course of several weeks he began to experience difficulty in swallowing and speaking and the twitching in the right arm became more pronounced. All of these symptoms increased in severity so that finally he could no longer talk, and he had extreme difficulty in swallowing. There was continuous drooling of saliva. He lost about twenty pounds in weight; his feet and hands became swollen. The last two months were marked by difficulty in breathing when lying down. He had been getting vitamin B₁ intramuscularly and intravenously once or twice a week for three months before he entered the hospital.

Examination. The patient is markedly emaciated. He is bedridden and appears chronically ill. His blood pressure is 135 systolic and 85 diastolic. He is alert, cooperative, and has good insight into his illness. His speech is dysarthric, and swallowing is very difficult. There is generalized muscular atrophy, more marked on the right side, including the intrinsic muscles of the hands and feet. There is generalized spasticity, also more pronounced on the right side with marked generalized hyperreflexia and bilateral ankle clonus. The superficial reflexes are absent. The Hoffman sign is present bilaterally, while the Babinski sign is equivocal on the right side. Fibrillations are present in all muscle groups, including those of the tongue and intercostal spaces.

Laboratory data. Cerebrospinal fluid: Initial pressure, 110 mm. of water; Pandy, 0; cells, 6 red blood cells per cu. mm.; globulin, negative; colloidal gold curve and Wassermann reaction, negative; total protein, 43 mg. per cent. Electroencephalogram, normal. Urine: creatine excretion, 885 mg. in 930 cc.; and 975 mg. in 930 cc. Blood: Hemoglobin, 13.5

grams; white blood cells, 5,600 with 68 per cent polymorphonuclear leucocytes; 28 per cent lymphocytes; 4 per cent monocytes. Wassermann reaction, negative; sugar, 95 mg. per cent; urea nitrogen, 10 mg. per cent. An electrocardiogram was reported as showing, "inverted P waves, low voltage of QRS complex, suggesting a vertically placed heart". A throat culture (May 8) grew: "streptococcus hemolyticus, streptococcus viridans, micrococcus catarrhalis, and diphtheroids".

Course. The diagnosis of amyotrophic lateral sclerosis with bulbar involvement was made and the patient was immediately placed on vitamin E therapy. He received 50.0 mg. a-tocopherol intramuscularly each day. He also received ephynol, wheat germ oil, vitamin B₁ and Brewer's yeast. Within twenty days the patient stated that his ability to swallow had improved and that he breathed easily although there were no objective signs to support this observation. He developed an acute pharyngitis during the course of which the weakness and fibrillations became accentuated. Pneumonia developed in the right lower lobe and he died two days after the development of the respiratory disease.

Necropsy findings. *Brain.* *Gross.* No gross changes could be recognized on sectioning the brain or spinal cord.

Microscopic. Sections of the cerebral cortex, midbrain, pons, medulla and spinal cord were stained with various neurohistological methods as were sections of the right intercostal, right pectoral and other muscles. The cerebral cortex exhibits degenerative changes of the large pyramidal cells. Their outlines are rounded and in some, there is a peripheral displacement of the Nissl substance. The nuclei show corresponding degenerative changes as indicated by their displacement and often complete disintegration. There is satellitosis often approaching frank neuronophagia. Similar, but more pronounced, changes are seen in the nerve cells of the hypoglossal nucleus and those of the anterior horns of the spinal cord (fig. 1). Myelin preparations reveal extensive demyelination of the pyramidal fibers. This is noted throughout the brain stem and the spinal cord. In the medulla oblongata the pyramids (fig. 2) show, in addition to loss of myelin, areas of disintegration in which both myelin and axis cylinders are lost (fig. 3). In addition, areas of demyelination are also seen in the region of the tractus gracilis where the fibers are about to terminate in the nucleus gracilis (fig. 2). In the spinal cord, demyelization is most pronounced in the lateral pyramidal tracts (fig. 4). Fat stains demonstrate a large amount of fat in the region of the cortico-spinal tracts in the midbrain, medulla, and in the lateral pyramidal tracts of the spinal cord (fig. 5), and to a lesser extent in the ventral pyramidal tract. An increased amount of fat is also found in the nerve cells of the inferior olivary nucleus and in the anterior horns of the spinal cord. Corpora amylacea are abundant in the dorsal, lateral and ventral funiculi of the spinal cord and in the brain stem at various levels including the midbrain,

pons, and medulla. The muscle preparations (fig. 6) display a large increase in the number of sarcolemma nuclei, a disappearance of striations,

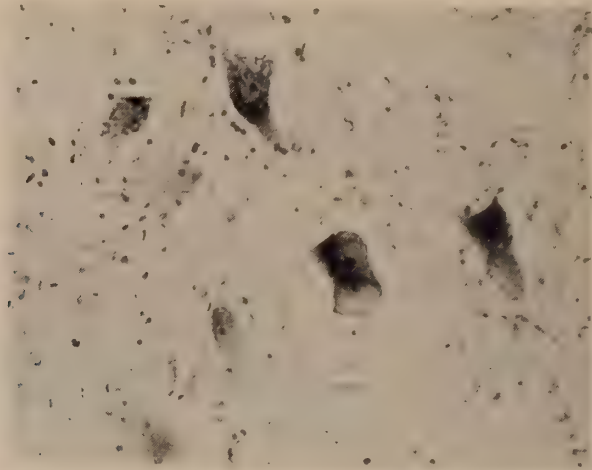


FIG. 1. Nerve cells in the ventral horns of the spinal cord showing advanced degenerative changes (amyotrophic lateral sclerosis), Nissl preparation.

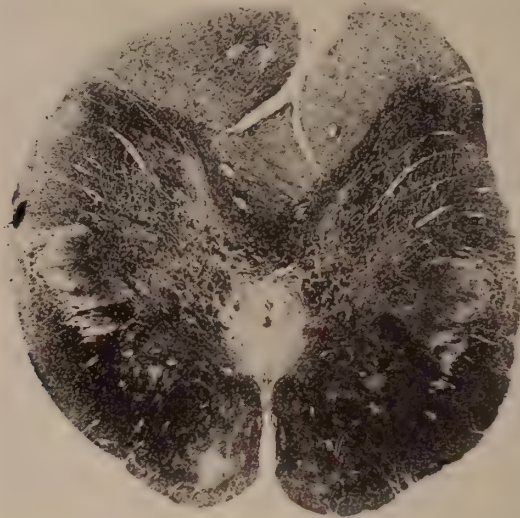


FIG. 2. Section of the medulla oblongata showing advanced demyelination of the pyramids with patchy-demyelination in the region of the tractus gracilis. Note the areas of disintegration in the pyramids, shown in figure 3, under higher magnification, myelin stain.

hyalinization of muscle fibers and great variability in the size of the muscle fibers; some are swollen, others shrunken.

Comment. Dr. Globus: The patient entered the hospital with the clinical

picture fully developed, leaving no doubt as to the diagnosis. The presence of both upper and lower neuron involvement and the evolution of the manifestations, beginning with an affliction of one extremity, rapidly progressing to assume a symmetrical distribution, are all features pointing to this diagnosis. The marked bulbar involvement, of course, indicated that little promise could be held for ultimate recovery.

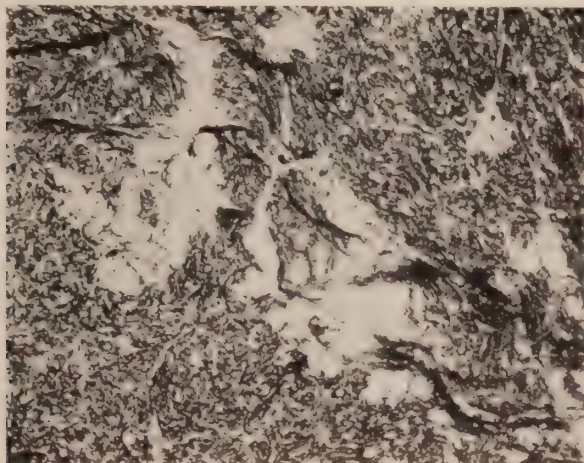


FIG. 3. Areas of disintegration in pyramids, myelin stain (see fig. 2).

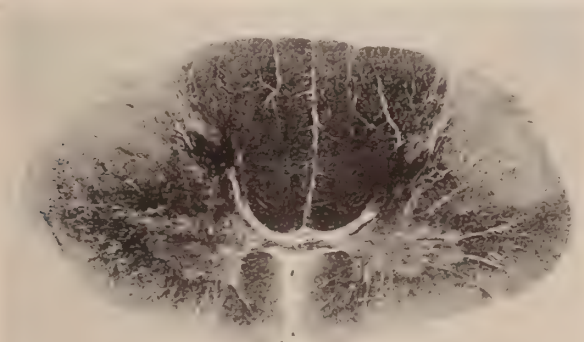


FIG. 4. Section of cervical spinal cord, showing demyelination of lateral pyramidal tracts in amyotrophic lateral sclerosis.

The disease as shown by the histologic studies is a form of primary dissolution of the neuroectodermal derivatives of the cerebrospinal axis, a form of primary degeneration affecting predominantly, but not exclusively (some changes were also found in the dorsal sensory tracts), the motor systems of the cerebrospinal axis; the upper (pyramidal) and lower (anterior) horn cells.

I have often wondered whether we are not dealing in this disease with some form of an involutional degenerative process affecting predominantly

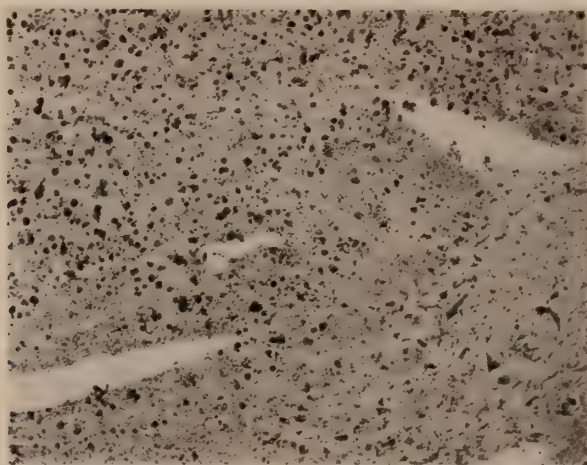


FIG. 5. A fat (Scharlach R) preparation displaying (coarse black granules) the breaking down of myelin into simple fats in amyotrophic lateral sclerosis.

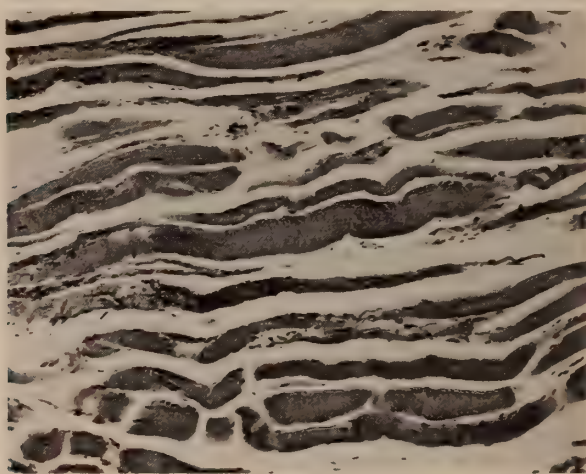


FIG. 6. Muscle fibers in amyotrophic lateral sclerosis (see text).

the motor (pyramidal) systems, in an organ, the life span of which has been predestined to be relatively short by virtue of some deficiency in its primordial material.

Reported by *B. Goldberg, M.D.*

Case 2. Craniopharyngeoma

[From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen]

History (Adm. 460376; P.M. 11568). A 33 year old Puerto Rican housewife entered the hospital on July 26, 1940. Six years previously she passed through a normal pregnancy which was followed by persistent vaginal bleeding, for which a laparotomy was performed. Her menses were regular for the next three and a half years until she became pregnant again. An induced abortion terminated the pregnancy and following this she became permanently amenorrheic. The next significant change took place six months prior to her admission to the hospital when she, rather suddenly, began to drink large quantities of water, averaging at least fourteen glasses a day. This was accompanied by pronounced polyuria, waking her seven to eight times each night to pass water. During the last month headaches made their appearance. They were aggravated by movement of the head. This was soon followed by vomiting which occurred when the headache was severe and was accompanied by nausea, dizziness, and epigastric pain. About this time she also began to complain of feeling feverish, of a bitter taste, of dulling of the sense of smell, and impairment of vision. Weakness set in and she would lie down for progressively longer periods each day.

Examination. The patient is a well developed, moderately obese woman, whose face is flushed and who complains of severe headache. The heart and lungs are negative. The blood pressure is 104 systolic and 60 diastolic, and there is a midline supra-pubic scar. Mentally she seems somewhat depressed, slightly irritable and at times lethargic. There is bilateral papilledema, which is more marked on the right side, and retinal hemorrhages.

Laboratory data. Blood: Hemoglobin, 100 per cent; red blood cells, 5,750,000; white blood cells, 8,000 with 70 per cent polymorphonuclear leucocytes, 20 per cent lymphocytes, 8 per cent eosinophiles and 2 per cent monocytes. The blood Wassermann reaction was negative. The blood chemistry findings were as follows: serum albumin, 5.0 grams per cent; serum globulin, 1.3 grams per cent; total protein, 6.3 grams per cent; cholesterol, 220 mg. per cent; ester, 135 mg. per cent; chlorides, 565 mg. per cent; phosphorus, 5.7 mg. per cent; calcium, 10.3 mg. per cent. Urine, negative. The Janney glucose tolerance test was normal and there was no sugar in the urines collected during the test. Cerebrospinal fluid: Globulin, negative; colloidal gold curve and Wassermann reaction, negative; total protein, 34 mg. per cent. X-ray examinations of the skull and chest were negative.

Course. A supra-sellar, midline lesion in the hypothalamic region was thought to be the most likely diagnosis. The basal metabolic rate was

minus 17 per cent. An electroencephalography was performed and revealed a large amount of delta activity but no cortical focus. This was thought to indicate increased intracranial pressure from a deep seated mid-line lesion. Gynecological consultation revealed a healed cervical laceration; the uterus and adnexae could not be palpated. A lumbar puncture (July 30, 1940) showed normal initial pressure and dynamics; clear cerebrospinal fluid; negative Pandy reaction and no increase in cells. A ventriculography was performed on August 6, 1940 and disclosed marked symmetrical dilatation of the lateral ventricles, while the third and fourth ventricles could not be visualized. A right fronto-parietal craniotomy was performed on the same day and the third ventricle was exposed, but no tumor was found. Sections of fragments of the cerebral cortex of the right hemisphere removed at the time of operation were reported as revealing no significant pathological alterations. Following the operation, the patient became drowsy, her temperature rose, she developed paresis of the left arm and leg, and became incontinent. Two days after the operation, temperature remaining high, a complete left hemiplegia developed and she passed into coma. An emergency re-exploration was performed. A small extra-dural clot was found. The right frontal lobe was retracted and the right optic nerve was exposed, but no neoplasm was seen. A lumbar puncture showed xanthochromic cerebrospinal fluid under increased pressure. The coma persisted, hyperpyrexia developed and the patient died two days after the operation on August 8, 1940.

Necropsy findings. Brain. Gross. There was a large defect in the cerebral cortex due to operative intervention which extended ventrally for some distance in the neighborhood of the posterior end of the fissure of Sylvius. The cerebral cortex surrounding the defect appeared dirty-grey in color and somewhat softened in consistency, while the adjacent cortex of the posterior frontal and anterior temporal regions was covered by clotted blood and adherent meninges. At the base of the brain a tumor was present in the interpeduncular region. It extended from behind the optic chiasm, which it had displaced anteriorly, throughout the entire extent of the interpeduncular fossa and disappeared under the anterior edge of the cerebral peduncles without its posterior limits being visible. It included the entire floor of the hypothalamic region, involving the infundibulum and tuber cinereum and the floor of the third ventricle. The mammillary bodies were not visible. The tumor had a fairly smooth outline and yellowish color. On palpation it was soft and gave the impression of being cystic. The infundibulum seemed much larger than normal and had a yellow cystic appearance. The pituitary seemed larger than normal and it was yellow in color and of a soft, cystic consistency.

On sectioning the brain, the tumor is found completely filling the third ventricle (fig. 7). It seems to be adherent to the floor and also part of the walls of the third ventricle, although it could be detached from the upper

part of the walls and the roof of the ventricle where it gives the impression of being encapsulated. The tumor is solid in consistency and presents a pearly white granular surface with a few small cystic areas filled with a grey gelatinous material. The tumor is continuous with an expansion at the base of the brain in the interpeduncular space.

Microscopic. Sections of the tumor stained with hematoxylin and eosin and by the Weil and Nissl methods show it to consist of an irregularly branching syncytial-like mass of strands and sheets of closely packed cells surrounded by a delicate connective tissue stroma (fig. 8 A). The cells are epithelial in appearance and have large, oval and clearly defined dark-staining nuclei. The outline of the clear staining cytoplasm of these cells is poorly defined except for the periphery of the cellular strands and sheets

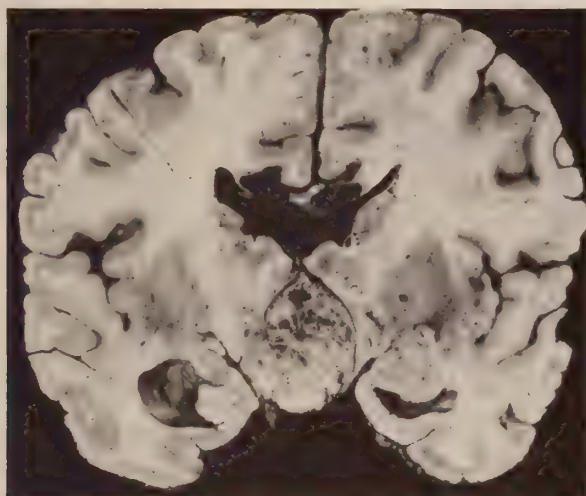


FIG. 7. Gross appearance of the tumor (craniopharyngeoma) in a coronal section of the brain.

where they form a regular row of uniformly sized cells, rectangular in outline. The cells frequently show papillary and acinar formations. The centrally placed cells often have a stellate shape giving rise to delicate processes assuming the appearance of cells in mesenchymal tissue; then again they appear to be rounded, their cytoplasm contains round globules, their nuclei are darkly stained and eccentrically placed.

Small blood sinuses and delicate connective tissue fibers are also seen in the center of the less densely packed cellular aggregations and the connective tissue surrounding these aggregations also has thin, scant fibers and blood sinuses.

Scattered throughout the center of the epithelial cell masses are small round collections of cells which are quite different in appearance (fig. 8 B). They consist of closely packed, somewhat flattened, oval or round cells

with clear pale pink cytoplasm, the nuclei of which are either faintly outlined or entirely absent. The cytoplasm of these cells appears keratinized and they represent collections of hornifying squamous epithelial cells.

The brain tissue is seen adjacent to the tumor and shows an increased number of glial elements and these together with the neighboring nerve

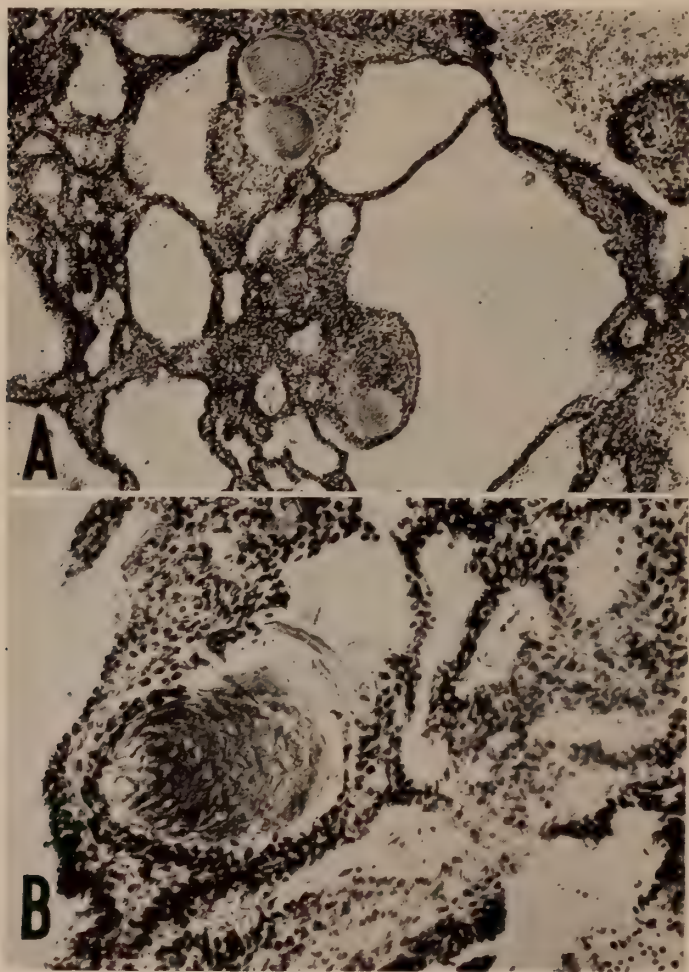


FIG. 8A. Histological appearance of the tumor (craniopharyngeoma). B. Epithelial (squamous) cell masses in craniopharyngeoma under higher magnification.

cells frequently show advanced degenerative changes. Small collections of tumor cells infiltrate the adjacent brain tissue. Silver stains reveal the argyrophilic nature of the connective tissue both within and outside of the islands of tumor cells.

Sections of the cerebral cortex, show it to be markedly edematous with

considerable disorganization of the cytoarchitecture. The nerve cells are swollen, show indistinct cell outlines, pale staining cytoplasm, eccentrically placed and vesicular nuclei. All the vessels are congested; many of the larger vessels show thickening of the vessel wall. There is an increase in the number of glial elements, especially in the subcortex.

Sections of what grossly appears to be the pituitary body reveal that the greatest part of the gland is composed of tumor. The latter shows the same structures as described above and has a fairly well defined connective tissue capsule. Closely applied to one side of this capsule is a small crescent-shaped mass of tissue representing the remains of the compressed and displaced pituitary body. The normal acinar arrangement of the cells is replaced by flattened ribbon bands of otherwise normal cells. The eosinophile, basophile and chromophobe cells are all present in relatively normal proportions.

Comment. Dr. Globus: Of significance in this case are: the abrupt cessation of menstruation, the subsequent development of polydipsia and polyuria, the subjective feeling of hyperpyrexia and signs of increased intracranial tension. The vegetative disturbances draw immediate attention to the cerebral visceral controlling centers, the existence of which in the floor of the third ventricle, the hypothalamic region of the diencephalon, is now quite well established (1). Placing these observations alongside the signs and symptoms of brain tumor: the papilledema, persisting headaches and repeated vomiting, the diagnosis of a cerebral neoplasm in the interpeduncular region becomes most logical. The rather long clinical course, the absence of alterations in the sella turcica and the failure to establish the presence of typical changes in the fields of vision, excluded a pituitary adenoma, and left a suprasellar expanding lesion in the nature of craniopharyngeoma as the diagnosis of choice. This was found to be in accord with the necropsy findings.

Reported by *A. Stein, M.D.*

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ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Lipiodol Granuloma in Fallopian Tubes Localized by Intra-uterine Diodrast Injection, with Special Reference to the Value of Follow-up X-ray Films. I. C. RUBIN. Radiology, 33: 350, September 1939.

Lipiodol injection into the uterus is frequently followed by retention of the iodized oil in the tubes as well as in the pelvic and upper abdominal cavity. Eighteen out of 27 cases in which a follow-up film was available showed opaque deposits at periods of from one month to one year and longer.

Retention is common when the tubes are sealed or partially patent. The damage is more serious in the latter cases in which the partially permeable lumen becomes obliterated by organization and foreign body granuloma. The value of follow-up films is emphasized. If a radiopaque substance is to be used, the crystalloid iodides have the advantage of being injected more than once and are especially useful for purposes of identifying lipiodol residue within the tube lumen.

Treatment of Cryptorchidism with Male Sex Hormone. C. ZELSON AND E. STEINITZ. J. Pediat. 15: 522, October 1939.

In attempting to improve the results heretofor obtained with gonadotropic hormone, twenty cryptorchid boys were treated with male sex hormone. Seventeen of the boys had unilateral cryptorchidism and three bilateral. Total dosage per boy varied between 60 and 180 mgs. Eleven of the boys had been previously treated with gonadotropic hormone with no effect. Of these, two responded to the testosterone treatment. There was complete descent in three cases, that is, 15 per cent of the entire group. The testosterone propionate had a partial effect on some of the children. There was enlargement of the penis in sixteen cases, enlargement of the scrotum in eight cases and a definite growth of pubic hair in ten cases. In five cases the testicles became smaller. It is concluded that gonadotropic hormone is more effective than male sex hormone. Those cases that show a partial response to male sex hormone should be followed with a course of gonadotropic hormone injections. A review of the literature on male sex hormone and the treatment of cryptorchidism with male sex hormone is included.

Movable Traction Carrier. A. M. ARKIN. J. Bone & Joint Surg. 21: 1032, October 1939.

An apparatus is described which is designed to allow the application of continuous traction to a lower extremity, the traction to follow in the line of the extremity as the hip is moved.

It consists of a fixed frame bolted to the bed, from which is suspended a movable frame in the shape of an inverted U which carries the traction. The two are connected by a hinge and swivel joint placed directly over the hip, so that the horizontal arm of the frame remains parallel to the thigh as the lower extremity is moved.

The Management of Pathological Fractures. E. M. BICK. Surg. Gynec. & Obst. 69: 524, October 1939.

Fifty-nine patients in whom 85 pathological fractures occurred were studied in reference to the effect of treatment on union. From this material it was possible to evolve certain rules or principles which should assist in formulating treatment applicable to pathological fractures in general.

Trauma is in itself always a stimulus to reparative osteogenesis in pathological fractures. The extent of repair in pathological fractures is a function chiefly of the density of pathological tissue displacing bone and/or the volume of displaced bone requiring replacement. Reparative osteogenesis can be stimulated greatly in selected cases by curettage of the pathological tissue and deposition of bone chips. In certain lesions such as giant cell tumor or bone cyst, in which union may occur under conservative care, this procedure will hasten and strengthen repair. Operation is especially indicated in cystic lesions or in those in which the pathological lesion merely permeates existing trabeculae. Union between the residual normal bone adjacent to a persisting lesion is an invitation to refracture. Whenever feasible its removal and replacement by bone chips is advisable.

Allergometric Tuberculin Study. H. VOLLMER, C. ZELSON, CARL AND H. RUBIN. J. Pediat. 15: 508, October 1939.

One hundred and six children with active tuberculosis have been tested, by varying dilutions of intracutaneous tuberculin and by an allergometric patch test administered simultaneously. The allergometric patch test compares favorably with the intradermal tuberculin test in that the results tend to show that individuals who react to the weakest dilution of the tuberculin given intradermally also react to the weakest solution in the filter paper patches. The severity of the tuberculin reaction does not indicate the severity of the tuberculous process in a group of children with active tuberculosis. The allergometric patch test could replace the original patch test, since it has the same qualitative value, and in addition, gives some quantitative information with regard to the individual sensitivity; if repeated at intervals, it will show the course of the tuberculin sensitivity.

The Management of Exophthalmic Goiter in a General Hospital. R. LEWISOHN, B. S. OPPENHEIMER AND S. SILVER. J. A. M. A. 113: 1527, October 1939.

Of the 460 patients with thyroid disease not operated on previously, who were treated surgically from April 1, 1932, to April 1, 1937, 360 cases belonged to the toxic group and 100 cases were nontoxic. The mortality (three cases) occurred in the toxic group. The mortality (including one suicide) was 0.8 per cent among the primary cases of exophthalmic goiter. Operative deaths numbered two (0.5 per cent) among the primary cases. There were two operative deaths among twenty-six cases of recurrent exophthalmic goiter. Twenty per cent of the patients were operated on in two stages.

Sarcoma of the Trachea. T. WEINBERG. Am. J. Cancer, 37: 201, October 1939.

Only 32 cases of sarcoma of the trachea are reported in the literature. The two cases reported by the author are the only ones encountered at The Mount Sinai

Hospital in the last ten years. The first case was a myxosarcoma, with a possible origin in a mixed tumor of the salivary gland type. The second case was a spindle cell sarcoma. The explanation for the production of stridor in these cases is interesting. The tumor invades and destroys the cartilaginous rings and the wall of the trachea partially collapses, causing a narrowing of the lumen. Attention is called to the relatively low malignancy of these tumors, death usually being due to the mechanical effects upon the respiratory system with production of a chronic anoxemia and subsequent cardiac failure.

Basal Metabolism of Tuberculous Children, III: Bone Tuberculosis. A. TOPPER. Am. J. Dis. Child. 58: 778, October 1939.

Previous studies of the metabolism of afebrile tuberculous children showed that the basal metabolic rate can be used diagnostically to determine the activity of a primary pulmonary infection.

The present studies were made to see whether this criterion of activity could also be used in bone tuberculosis.

It was found that in tuberculosis of bone, the general metabolism remains normal, irrespective of whether the process is inactive, or active with draining sinuses. When the condition, however, is associated with active primary tuberculosis of the lung, the basal metabolic rate is elevated.

These studies emphasized the fact that an increased basal metabolism in the presence of a normal temperature can be used as an additional criterion of activity of a primary pulmonary lesion. Further, when an afebrile child with bone tuberculosis is found to have an elevated metabolism, the presence of an active primary pulmonary lesion should be suspected.

The Determination of Vitamin C in Children by Intradermal Injection. H. G. RAPA-PORT AND S. H. MILLER. J. Pediat. 15: 503, October 1939.

A series of 100 children were injected intradermally with a dichlorophenolindophenol solution, and a bluish wheal was produced. The length of time for the blue color to disappear was noted. The ascorbic acid of the blood plasma was determined by the Farmer and Abt method, and the authors attempted to correlate the time taken for the dye substance to decolorize with the amount of vitamin C in the blood plasma. There is no satisfactory correlation which can be used for clinical purposes.

Scoliosis Following Empyema. S. SELIG AND S. ARNHEIM. Arch. Surg. 39: 798 November 1939.

This study was undertaken because of the impression that scoliosis was an occasional sequel to operations for empyema. All cases of non-tuberculosis empyema operated upon during the years 1932-1936 who could be reached for follow-up examinations were included in the study (sixty-five cases).

Five of the sixty-five patients had evidence of scoliosis which was severe in only two cases. Thirteen of the sixty-five patients had chronic empyema and all the scolioses appeared in this group. However, other cases of chronic empyema beginning in childhood did not develop scoliosis. Persistent scoliosis is not a complication of acute empyema, but may occur as a complication of chronic empyema in children.

Peritonitis in Cats Produced by Intraperitoneal Injection of Bacillus Coli Suspended in Mucin. G. P. SELEY. Arch. Surg. 39: 783, November 1939.

In this paper there is presented an easy method of producing experimental B. coli peritonitis in cats. Numerous attempts have been made to produce bacterial peritonitis in animals. Because of considerable irregularity of the results obtained

by most of these previous methods, an effort was made to develop a standardized method for producing experimental peritonitis. Previous investigators have reported the successful use of mucin to increase the virulence of induced bacterial injection in mice and rats. After preliminary work with mice, rats and rabbits, a simple method of producing fatal suppurative bacterial peritonitis in cats was developed. A human strain of *B. coli* suspended in mucin, when injected intraperitoneally, invariably proved fatal. The minimal lethal dose was 63,000,000 organisms. This method is at present proving valuable in further studies on various methods of prevention and treatment of experimental peritonitis.

Treatment of Venereal Lymphogranuloma with Sulfanilamide. A. W. M. MARINO, R. TURELL, A. M. BUDA AND L. NERB. *Am. J. Surg.* 46: 343, November 1939.

The authors treated successfully two patients with anorectal and one with inguinal (glandular) manifestations of venereal lymphogranuloma with sulfanilamide in large doses under hospital control. A concentration of 5 or more mg. of free sulfanilamide per 100 cc. of blood is arbitrarily advocated. A comparative study was made utilizing three clinic ambulatory patients. In one of these patients the concentration of sulfanilamide in the blood was only 1 mg. free sulfanilamide per 100 cc. after the supposed daily administration of 3.5 gm. of sulfanilamide until 50 gm. were supposed to have been taken, showing that ambulatory patients cannot be entrusted with important therapy. Sulfanilamide exerted the most pronounced effect on the inflammatory and suppurative processes. The authors emphasized that a precise plan of sulfanilamide therapy for these patients has not yet been evolved.

Basal Metabolism of Tuberculous Children, IV: Children with Pneumothorax. A. TOPPER AND H. S. RUBIN. *Am. J. Dis. Child.* November 1939.

Studies were made of the basal metabolism of children in whom pneumothorax therapy had been instituted. The average basal metabolic rate before pneumothorax was plus 7 per cent.

From 1 to 6 months later, the average B.M.R. had fallen to -3 per cent; from 6 to 12 months later, the average was -5 per cent. In children in whom collapse therapy had been maintained for more than 1 year, the average basal metabolism was -12 per cent.

These studies indicate that the basal metabolism is lowered by pneumothorax therapy. The longer the pneumothorax is maintained, the lower the metabolism seems to fall.

Studies of the vital capacity of these children gave results 37 per cent lower than the expected normal.

Experimental Biologically Active Ovarian Tumors in Mice. S. H. GEIST, J. A. GAINES AND A. D. POLLACK, M.D. *Am. J. Obst. & Gynec.* 38: 786, November 1939.

Through the medium of x-ray irradiation of mice at puberty two types of ovarian tumors are produced: tubular adenomas derived from the surface epithelium and parenchymal lutein tumors. The latter neoplasms exhibit hormonal (estrogenic) activity, expressed in proliferative changes in the endometrium and vaginal mucosa. Histologically, they are composed of granulosa and theca cells with varying degrees of luteinization.

The histogenesis of these neoplasms was studied by periodic sacrifice of the animals from puberty to senescence. The luteinized ovarian tumors were found to be derived from undifferentiated parenchyma. While the theca interna cells anticipate in the early proliferation and luteinization, the mature granulosa cells play no role in the genesis of these neoplasms.

The histogenesis of analogous human tumors may well be identical.

The Hemato-Encephalic Barrier. I: A Study of the Clinical Aspects and the Mechanism of Development of Hypertension of the Cerebrospinal Fluid in Hypertensive Disease. M. M. KESSLER, E. MOSCHOWITZ AND N. SAVITSKY. *J. Nerv. & Ment. Dis.* 90: 5, November 1939.

Cerebrospinal hypertension occurs frequently in the late stages of hypertensive disease, whether of essential origin or that associated with glomerulonephritis. Clinically, this phase is characterized by headache and papilledema. In most instances the patellar reflexes are exaggerated and sometimes there is exophthalmos. Unless a high cerebrospinal pressure can be demonstrated any headache in hypertensive disease must be viewed with suspicion as possibly the result of other causes. The papilledema of hypertensive disease is never an isolated retinal phenomenon but is always associated with the arteriosclerotic and exudative lesions, and represents the terminal event of a biological process. In the pathogenesis of papilledema of hypertensive disease three factors enter; (a) an increased permeability of the hemato-encephalic barrier, (b) an increased venous pressure, and (c) an increase in cerebrospinal pressure. These agents may act separately, mutually or consecutively. In the mechanism of development of cerebrospinal hypertension in hypertensive disease the volume of the brain and spinal cord, owing to the Monroe-Kellie doctrine, is of negligible importance. The increase in cerebrospinal pressure is caused by two factors; (a) a sustained increase in venous pressure, and (b) increase in permeability of the hemato-encephalic barrier. These factors act separately or consecutively. Increase in venous pressure causes increase in cerebrospinal pressure either directly by causing engorgement, or indirectly by increasing the permeability and therefore the quantity of cerebrospinal fluid. An increase in permeability of the hemato-encephalic barrier is practically the rule in advanced hypertensive disease. When such an increase is demonstrated, the patient reveals clinically the most advanced symptoms and signs; headache, papilledema and cerebrospinal hypertension are nearly always present. Increase in permeability bears no consistent relation to disturbance of renal function or to the genesis of the hypertension. In all probability the increased permeability of the hemato-encephalic barrier, when not complicated by increase in venous pressure, is due to capillary disease, most likely sclerosis, within the barrier. Systemic arterial pressure, no matter how high, does not directly increase the cerebrospinal pressure. Indirectly its influence may be very profound by inducing an increase in venous pressure. Osmotic changes resulting from disturbed metabolism (electrolytes and protein) in hypertensive disease have little or no effect upon the cerebrospinal pressure.

Acetanilid Poisoning. A. LESLIE. *J. A. M. A.* 113: 2229, December 16, 1939.

The interesting feature of the case presented was the disappearance of the headache on withdrawal of the acetanilid containing "Bromo-Seltzer", which had been self-administered for migraine. This patient had taken about 1.2 gm. of acetanilid daily for several years and 4.0-5.0 gm. daily for two months.

The semi-coma, in which the patient was first seen, was quickly relieved by administration of abundant fluids.

Headache can actually be produced by continued consumption of acetanilid, and with further consumption of the drug in an effort to relieve the pain, a vicious circle is set up. This is easily broken by complete withdrawal of the drug.

Heavy Oxygen Exchange Reactions in Proteins and Amino Acids. H. SOBOTKA AND W. H. MEARS. *J. Am. Chem. Society*, 61: 880, 1939.

The oxygen exchange behavior of proteins and protein derivatives was studied by means of water with high or low O^{18} abundance. The only oxygenous group in

amino acids which exchanges its oxygen against that of water was found to be the carboxyl group at acid reaction. Albumin at neutral reaction did not exchange any oxygen, but crystalline pepsin, as representative of a protein soluble at strongly acid reaction, exchanged 13% of its oxygen. This figure corresponds with the amount of oxygen present in the free carboxyl groups of the dicarboxylic amino acids contained in pepsin. The data, in addition to their bearing on the use of heavy oxygen isotopes in metabolic studies, add to our present knowledge of amino acid distribution in pepsin. This investigation was supported by a grant from The Rockefeller Foundation.

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CONTENTS

	PAGE
THE BIOLOGICAL RÔLE OF THE STEROIDS AND THEIR BEARING ON CLINICAL MEDICINE. <i>Harry Sobotka, Ph.D.</i>	255
THE ESTROGENS. <i>Robert T. Frank, M.D.</i>	269
VITAMIN THERAPY IN RAYNAUD'S DISEASE. Preliminary Report. <i>Rose Spiegel, M.D.</i>	284
AN INTRA-GROUP HEMOLYTIC TRANSFUSION REACTION DUE TO THE Rh AGGLUTINOGEN AS A RESULT OF ISOIMMUNIZATION IN PREG- NANCY. <i>Max Mayer, M.D., and Peter Vogel, M.D.</i>	300
LYMPHOSARCOMA OF THE STOMACH. <i>Harry Yarnis, M.D.</i>	305
CLINICAL PATHOLOGICAL CONFERENCE.....	308
CLINICAL NEUROPATHOLOGICAL CONFERENCE.....	312
ABSTRACTS	320

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THE BIOLOGICAL RÔLE OF THE STEROIDS AND
THEIR BEARING ON CLINICAL MEDICINE¹

HARRY SOBOTKA, PH.D.

[Chemist to The Mount Sinai Hospital, New York City]

I shall not attempt to talk tonight about the chemical constitution of the steroids and thereby burden you with elaborate and complex structural formulas. Nor shall I go into the history of the chemical discoveries which led to the recognition of the steroids as a distinct class of chemical compounds.

The steroids are a group of organic substances of plant and animal origin. They contain no nitrogen, but only carbon, hydrogen and oxygen. They are distinguished by a so-called condensed ring system, which consists of four interlocked rings, three of which have six carbon atoms and the fourth one five carbon atoms. This ring system was recognized by Rosenheim and King in London in 1932 as the true nucleus of the sterols, the bile acids and the female sex hormones, the chemical study of which had just at that time superseded purely physiological studies. A catalog of derivatives belonging to this group, which I had prepared at that time, comprised less than 400 substances. Dr. Rosenheim encouraged me to publish this catalog of chemical and physiological properties of the then known sterol derivatives in the light of the new formula. Then something disconcerting happened. While I was working on the manuscript, more and more publications appeared in rapid succession announcing the steroid nature of known and of newly discovered natural products, including all the substances listed on the diagram. By 1937, the number of steroid derivatives had risen to 4000, and the mere cataloging of their formulas and chemical constants filled a heavy volume (1).

The biological rôle of the sterids, or steroids, is so varied in nature that its discussion leads into endocrinology, pharmacology, vitamin research, the study of malignant tumors and problems of metabolism in general. I shall therefore ask you to bear with me as we travel back and forth across this map (fig. 1). It might seem that the only feature which unites the steroids is their chemical similarity, but there are some connections between them of a deeper nature, which await detection and elucidation. There certainly is no doubt that the clinician will encounter steroid compounds more and more frequently and will want to recognize them on sight.

I have asked myself the question, "What trait that distinguishes the

¹ The first in A Series of Lectures on the Steroid Hormones delivered at the Blumenthal Auditorium of The Mount Sinai Hospital, New York, March 7, 1941.

steroids has qualified them for the performance of so wide an array of physiological functions as is indicated, for instance, by the titles of the lectures in this series?"

There are three big groups of organic compounds which comprise, by a tremendous margin, the bulk of existing animal and plant tissue. These groups, proteins, carbohydrates and fats, are in constant exchange with the inorganic world, through the agency of carbon dioxide, water and ammonia as the main carriers of respiratory and digestive metabolism. The same goes for water, inorganic salts and the minerals making up the skeleton. The organic substances mentioned belong, by and large, to the straight chain or aliphatic type. If we now scrutinize live matter for the occurrence of cyclic compounds, there are a few surprises in store for us. The total amount of cyclic compounds in organic nature is probably less than one per cent by weight. Single rings occur in tyrosine and a few other amino acids, and these aromatic amino acids belong to the most essential and important constituents of proteins, and perhaps determine the shape and magnitude of the protein molecule. By slight modifications, they give rise to the hormones adrenaline and thyroxine. Single rings also occur in the terpenes and essential oils of widespread occurrence among plants; also in the carotenoids, including the vitamin A group, and finally in the fertility vitamin, tocopherol.

The naphthalene nucleus, consisting of two condensed rings, is very rare. It occurs only in vitamin K and in some sex hormone-like substances in lower animals. The anthracene type, three condensed rings, is known only in some rare plant products, for instance, some cathartic drugs.

Of the many possible systems consisting of four rings, by far the most important is cyclo-penteno-phenanthrene, the parent substance of the steroids. The steroids comprise only a fraction of one per cent of the body weight, but they are of a very solid structure, persisting long beyond the death of the individual and long after carbohydrate, protein and fat have decomposed. The preferential formation of this cyclo-penteno-phenanthrene nucleus, to the complete exclusion of other four-ring systems, and in amounts surmounting that of all other cyclic substances combined, testifies to the great stability of the steroids. This empiric impression of sturdiness will eventually be borne out by thermodynamic evidence, as well as by the interpretation of its molecular morphology, or one should perhaps say, molecular architecture. Obviously, the constitution of the steroids combines a maximum of stability with a maximum of potential reactivity, and by an assortment of substituents and side chains, the steroid molecule may be directed into pivotal points in organs, tissues and cells as its sphere of action.

In order to acquaint you with the various functions of steroids, I have prepared this diagram, which I shall use for two purposes. First, it is to serve as a sort of table of contents for this series of lectures. The inner

circle comprises the animal steroids, the outer circle the plant steroids. Both are arranged so that the number of carbon atoms decreases when we proceed in a clockwise sense. Cholesterol, the typical sterol of higher animals, has 27 carbon atoms. The bile acids have 24 carbon atoms, but the bile of the shark contains a substance called scymnol with 27 carbon atoms. A further shortening of the side chain leads to two groups of hormones with 21 carbon atoms, the corpus luteum hormone, which will be the subject of Dr. E. C. Hamblen's lecture² on April 30, and the hor-

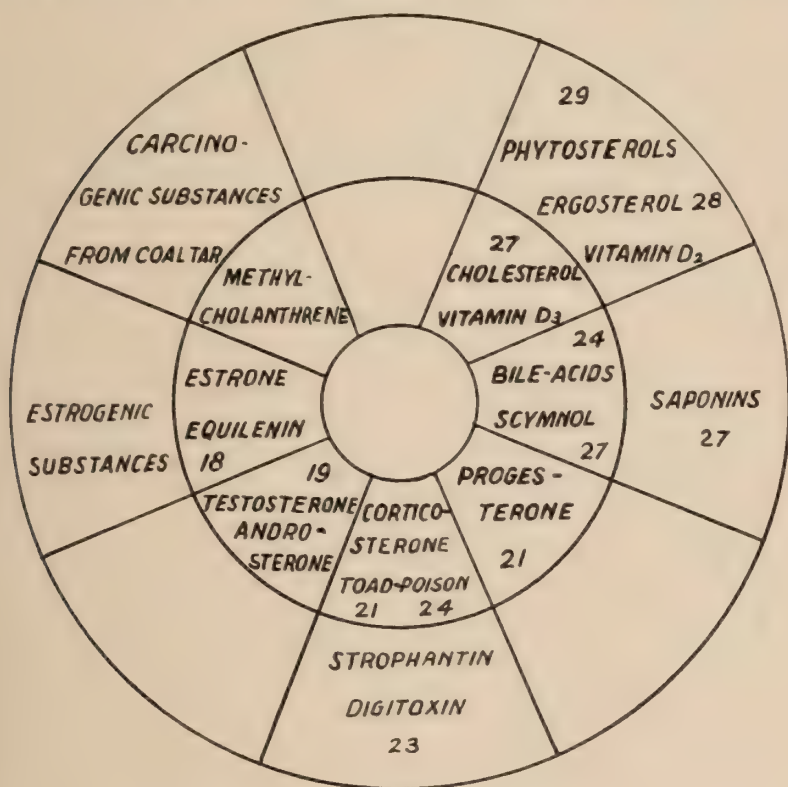


FIG. 1. Diagram of interrelationship of steroids

mones of the adrenal cortex, including their artificial derivatives such as desoxycorticosterone, which will be discussed by Dr. George W. Thorn³ a week from today. Complete absence of the long side chain characterizes the male hormones, which will be discussed on April 28. Loss of another carbon atom, by which the molecule is practically stripped to the bare cyclo-penteno-phenanthrene nucleus, and the simultaneous occurrence of three double bonds leads to the estrogenic substances with 18 carbon atoms,

² To be published in this JOURNAL, Vol. VIII, No. 6 (March-April), 1942.

³ To be published in this JOURNAL, Vol. VIII, No. 5 (January-February), 1942.

on which you will hear Dr. Robert T. Frank⁴ a month from today. For reasons to be discussed later, we have included methyl-cholanthrene as a representative of carcinogens of steroid structure, which, however, carry an even greater number of double bonds than the partly unsaturated estrogens. The special account of the carcinogens by Dr. C. P. Rhoads⁵ will conclude this series on May 12.

Many of the groups of animal steroids have their counterpart amongst plant steroids. Great similarity with cholesterol is exhibited by the phytosterols of the higher plants and the fungisterols, such as the ergosterol of ergot, yeast and other micro-organisms. A few families of plants elaborate soap-like substances designated as saponins in their seeds. The saponins are combinations of sugar with so-called sapogenins, and these sapogenins are steroids. The saponins are extremely surface-active and in this respect resemble the bile acids. Their surface activity has been used occasionally as a means of promoting diffusion of therapeutic agents, but the significance of these plant glucosides for the modern clinician is minimal in comparison with that other great group of plant steroids, the cardiac glucosides.

The cardiac glucosides consist likewise of a few sugar molecules bound to a steroid, which is again called a "genin." While the genins are most important for chemical structural investigations, much greater pharmacological activity is exerted by the glucosides. The hydrolysis of the glucosides by chemical means, such as acids, or by specific enzymes leads to the genins, and to avoid this hydrolysis, special precautions must be taken in the collection and drying of the plant leaves. The knowledge of these procedures goes far back into the folk-lore of civilized peoples and savages, familiar with the beneficial as well as the poisonous action of these glucosides. The most important effect common to these drugs is on the heart. This effect is exploited on the greatest scale in digitalis therapy (2). Minimal quantities of digitalis preparations enable a weakened heart to perform much more mechanical work without exhausting its reserve power, and to a great extent to overcome impaired oxygen supply. The emergence of digitalis therapy on a scientific basis about 100 years ago pushed into the background the use of related plant products such as strophantus, the related ouabaine and the slightly differently constituted squill glucosides. Differences in the chemical structure both of the sugar and of the genin moieties of these substances modify their effect on the heart. Digitalis, for instance, is rather insoluble; easily fixed to the tissues, its action is cumulative and of slow onset. Strophanthin, on the other hand, because of its greater solubility, acts immediately, is not fixed and not pronouncedly cumulative; hence its use in conservative amounts in cases of acute heart insufficiency that have not been treated with digitalis is a valuable addition

⁴ Dr. Frank's lecture appears in this issue of the Journal, pg. 269.

⁵ To be published in this JOURNAL, Vol. IX, No. 1 (May-June), 1942.

to heart therapy. The so-called digilanids, in recent years obtained by Stoll (3) from *digitalis lanata*, a variety of foxglove, again differ in action from *digitalis* and *strophanthin*, the two extreme types mentioned before. Other cardiac glucosides of exotic origin, such as thevetin, likewise deserve the consideration of the pharmacologist and of the cardiologist, and I do not doubt that the recognition of their chemical structure will eventually lead to synthetic steroids with cardiac action made, as it were, to the order of the physician.

On the diagram I have placed the toad poisons, animal steroids with 24 carbon atoms, in the same sector with the cardiac glucosides, because of their similar pharmacological and toxicological character. Attempts to deepen our knowledge of the mechanism of action of cardiac glucosides have recently led to observations on their effect on the potassium metabolism (4), and this, if confirmed, would justify placing them in the same sector with corticosterone, the hormone of the cortex of the suprarenal gland.

I wish to mention in passing that estrogenic and also androgenic effects have been observed in certain plant extracts, which may logically be attributed to steroid substances. You will hear more about this in Dr. Frank's lecture.

Little or nothing is known about the botanical counterparts of the other steroid hormones, and there are some blank spots to be filled in yet. For the sake of completeness I may remark that I am not aware of any report on carcinogenic action of steroid or hydrocarbon extracts from live plants (the effect of the alkaloid, colchicine, is of a different nature). The carcinogenic hydrocarbons originally obtained from certain coal tar fractions may, however, be considered as secondary products derived from fossil plant constituents.

We shall now return to the animal steroids. A substance related to the steroids but of somewhat different chemical structure is lanolin, *adepts lanae*, obtained from sheep wool. Its occurrence in the company of, and in mixture with, true fats reminds one of the true sterols, and so does its general physical character. While not water-soluble of itself, it tends to mix without separation with a multiple of its own weight of water. This makes it suitable as a carrier for salves and ointments. Lanolin and some artificial oxidation products of cholesterol, which have similar properties, are thus widely used in dermatological therapy and for related purposes as bland carrier substances.

The true sterols find their best known and most important representative in cholesterol. It was first isolated and recognized as a chemical individual by Poulletier de la Salle and then by Chevreuil, who obtained it from cadaver fat, from spermaceti and from gall stones; hence its name, "chole" meaning bile in Greek, and "stereos" solid.

Our knowledge of cholesterol forms a strange mosaic. Because of the

rather accurate methods of quantitative analysis, there is a wealth of data on the concentration of cholesterol in all body fluids and tissues under physiological and pathological conditions. But between these data are stretches of unknown territory, where extremely little is known regarding the function of cholesterol in health or disease, or the significance of its increases and decreases; less yet is known about the mechanisms by which cholesterol influences metabolic processes. Like lanolin, to which I compared it before, and on the other hand like lecithin and other phosphatids, whose physiological function is equally puzzling, cholesterol is not water-soluble in the strict sense of the word; however, as a rule without forming a visible emulsion, it occurs in dispersed form in the body fluids, where it and the proteins influence each other's solubility. Because of this dual nature, intermediary between water-soluble and lipoid-soluble substances, cholesterol is especially apt to occur on surfaces and interfaces, where it may arrange itself in monomolecular layers. When working with Dr. Langmuir on the properties of cholesterol layers one molecule thick, I calculated that red blood corpuscles in one cubic centimeter of blood have a combined surface of 7,000 square centimeters (about eight square feet). To cover this area with a monolayer of cholesterol requires about as much cholesterol as is contained in the dissolved state in the surrounding blood plasma (about 2 mg.). This relationship may be important in nephrosis, where the blood contains an increased amount of cholesterol and where the blood corpuscles display enhanced resistance to hemolysis (5). The property of lipemic sera, which are also rich in cholesterol, to putrefy less easily than normal serum is perhaps due to similar surface phenomena.

We find the cholesterol level of the blood definitely increased in biliary obstruction, which will be discussed a little later; this is true also in diabetes, starvation, pregnancy and in nephrotic conditions, the rare true lipoid nephrosis and the more frequent nephrotic stages of glomerular nephritis, conditions in which cholesterolemia is associated with increase of the other lipoids in the blood. The hypothesis has been advanced that in all these instances the cholesterolemia is a response to hypoproteinemia, the latter arising either from the loss of albumin by albuminuria or starvation or, in pregnancy from the greater hydration of the circulating blood of the mother in adaptation to the lower protein content of the fetal blood, as Dr. J. Novak has pointed out to me. The lowering of the colloid-osmotic pressure of the serum in these cases is perhaps counteracted by the colloid-osmotic pressure of the lipoids.

The liver plays a significant rôle in cholesterol metabolism. This is evidenced by the drop of blood cholesterol in parenchymatous liver disease as long as biliary obstruction is absent. The lowering of the serum cholesterol is considered typical, together with the lowering of other serum lipoids, in hyperthyroidism, while, on the other hand, cholesterol is high in hypo-

thyroidism and after experimental thyroidectomy, e.g., according to experiments by Fleischmann at Johns Hopkins (6). Much observational material has been gathered on the cholesterol level in eczema and various allergic conditions, but one could hardly venture beyond the general statement that there is a concatenation between cholesterol, protein metabolism and liver function.

Cholesterol carries an alcoholic hydroxyl group which permits its combination with fatty acids, such as oleic or palmitic acid, to form cholesterol esters. In normal individuals two-thirds to three-fourths of the cholesterol is in the esterified form. In parenchymatous liver disease, especially in liver atrophy, in acute episodes of liver cirrhosis and during the later stages of prolonged biliary obstruction, the ester percentage drops and may reach zero; that means complete absence of cholesterol esters in the terminal stages of these conditions. The determination of the cholesterol esters and the observation of this ester-drop by Thannhauser was extensively studied in our own laboratory by E. Z. Epstein (7). The increase of the ester fraction in blood on standing has been observed by Sperry (8) and suggests a complex interaction between enzymatic synthesis and hydrolysis in the liver and the blood.

In addition to these wide deviations of blood cholesterol in acute disease, we must also consider disturbances of cholesterol metabolism which may not always be mirrored by a change in the blood level of cholesterol. Dr. Thannhauser will discuss on March 24 some of the clinical aspects of cholesterol metabolism in connection with xanthomatosis. Cholesterol accumulates specifically in certain body tissues, (a) in the majority of human gall stones, (b) in atheromatous lesions in arteriosclerosis, (c) in the cholesterol type of lipoidosis, so-called Schueler-Christian disease, and in xanthomata, xanthelasmata, arcus senilis, etc. It is remarkable that in the conditions mentioned the deposition of cholesterol is usually accompanied by the deposition of carotene, whose only known biological function is that of precursor to vitamin A. There is no simple correlation between the occurrence of gall stones or of sclerotic lesions and the incidence of a high cholesterol level in the blood, but xanthomatous lesions and xanthemia are usually associated with high cholesterol values.

I am convinced that the blood cholesterol values cannot tell us the whole story, but sometimes gives us a distorted cross-section. Three factors deserve consideration in this regard.

(a) Because of the interrelation of cholesterol solubility with other colloidal serum constituents, primarily proteins and perhaps the phosphatids, it may be desirable, although at present not practicable, to consider cholesterol saturation and capacity rather than absolute cholesterol content (9). The tendency for cholesterol to form pathological deposits may depend on the capacity of the serum to carry small or larger amounts of cholesterol and on the relation of this capacity to the cholesterol actually carried.

Tests for the study of these conditions have been developed but have not yet found general acceptance.

(b) A study of the diurnal variations of the cholesterol level in relation to time and composition of meals makes obvious the importance of the nutritional state of the individual. Cholesterol exerts a carrier function for fatty acids, which perhaps explains its rise in the blood during inanition, when it helps in the mobilization of peripheral fat depots.

(c) Cholesterol results often appear erratic in spite of elaborate analytical methods, and one finds in a series of hundreds of cases of supposedly normal controls a considerable number of values between 250 and 400 milligrams per cent, regardless of the method used, while the majority of the cases conforms to a level of 180 to 220 milligrams per cent. A recent study of a large family by Svendsen (10) offers the interesting suggestion that there exists a gene for the high blood cholesterol group, and that in every instance of a so-called "unjustified" high cholesterol value, a similarly high value will be found in at least one of the parents.

Another aspect of cholesterol metabolism concerns the presence of cholesterol in the bile. The bile, as excreted by the liver, contains 50 to 100 milligrams per cent of cholesterol, all in the non-esterified form. The significance of its presence is unknown, but we do know that under certain abnormal conditions, especially in infection and when the bile becomes more acid than ordinarily, the bile loses its dissolving power for cholesterol, resulting in the formation of cholesterol stones. The history of these stones varies, and it is an interesting task to compare the concentric stratification, the inclusion of protein and pigmented layers with the recorded disease symptoms. Similar to the methods of the geologist, the clinical history can be reconstructed from the mineral record.

Often gall stones cause obstruction not only sealing off the gall bladder, but interrupting the flow of the bile through the ductus hepaticus and communis into the intestine. Similar obstruction, caused by inflammation or by neoplasms, results in regurgitation of the bile through the liver into the blood stream. The resulting jaundice is accompanied by hypercholesterolemia. The naïve conception that this increase of the cholesterol level in the blood is due to the accumulation of cholesterol, which otherwise would be excreted as such in the bile flow, does not stand up under mathematical analysis. One often may observe a rise from 250 milligrams per cent to more than twice this value within a few days. If one tried to account for this amount by the biliary cholesterol, such a rise would take a minimum of four to six weeks. What I consider the correct explanation leads us into the field of the bile acids, which, as you see indicated on the table, contain three fewer carbon atoms than cholesterol. It is easy from the chemical viewpoint to imagine that bile acids originate from cholesterol or from a common precursor. ■

According to an estimate which I shall substantiate presently, the liver

produces about three grams a day of bile acids under normal conditions, to make up for the loss through the feces. In biliary obstruction, when no bile and no bile acids reach the intestine, this production seems to stop abruptly. A simple computation shows that the regurgitation of four hours' output of bile acids into the circulation would cause lethal bile acid poisoning. Of course, bile acids do reach the blood stream and hence the urine in increased quantities at the onset of obstruction, but the actual amounts are minimal compared to the productive capacity of the liver. Thus, it seems that the rapid increase in the serum cholesterol takes a vicarious place and demonstrates a qualitative shift from the production of the one steroid group, the bile acids, to another steroid group, cholesterol.

The bile acids and their sodium salts, the bile salts, are a group of steroids which has attracted the attention of physicians since Biblical times. Certain therapeutic effects of bile were known in antiquity. Its detergent action and perhaps bactericidal effect upon organisms of the pneumococcus type, the so-called Neufeld phenomenon, were known to the angel who appeared to Tobias (11) and advised him to use fish bile to cure his father's blindness, which was presumably due to some pneumococcus-like infection common at the time and place. Another therapeutic effect of the bile, due to its content of bile acids, is its cathartic action when given *per os* or rectally. Finally, bile preparations have been used, on and off, to stimulate bile production itself. The numerous other drugs besides bile salts which affect the bile flow are inorganic salts, alkaloids, synthetic drugs and physiological agents like hormones. Digestion, starvation, gestation and lactation likewise influence the bile flow in a number of ways. The variables are the total volume of the bile, its acidity and the absolute and relative constitution of its main components.

We have mentioned cholesterol before as one of them. Mucin, which functions as a lubricant of the bile passages, and the bile pigments, primarily bilirubin, which may be considered a purely excretory product, are other bile constituents. However, it is the bile acids, the most important ingredient of bile, which earn it the name of a secretion rather than an excretion and make it one of the important digestive juices. They are of great variety and show interesting variations from one species of animal to another in their chemical constitution. Bile acids are produced by practically all vertebrate animals with the exception of the cartilaginous fish, the shark, whose bile contains the neutral steroid, scymnol.

The bile acids come from the liver in the conjugated state. What is conjugation? Conjugation is the combination of a water-insoluble substance with a group that imparts to it greater water solubility. We have mentioned that the plant steroids both of the saponin and of the cardiac group are made more soluble by conjugation with sugars. Toad poison is conjugated with suberic acid and the amino acid, arginine. Conjugation is used by the body for all sorts of detoxification processes, as in the excre-

tion of benzoic acid as hippuric acid, of cinnamic acid as cinnamoyl glycine (12). This conjugation mechanism is located according to species in liver or kidney. It is easy to understand that this mechanism is also used in order to increase the solubility of bile acids, and hence their efficiency as emulsifying agents in the resorption of fats from the intestine. The free bile acids, cholic acid and the especially effective deoxycholic (or desoxycholic) acid, are conjugated with the amino acids, glycine or taurine, to form glycocholic acid, taurocholic acid, etc. The analysis of the bile acids offers great difficulties. A whole system of analytical procedures to differentiate between the various bile acids obtained from fistular bile has been devised by Doubilet (13) in these laboratories. The determination of the bile acids, as to quantity and quality, in the blood stream still offers immense difficulties.

Bile is excreted from the liver approximately as a two per cent solution of bile salts with a pH of about 8. During the stay in the gall bladder the

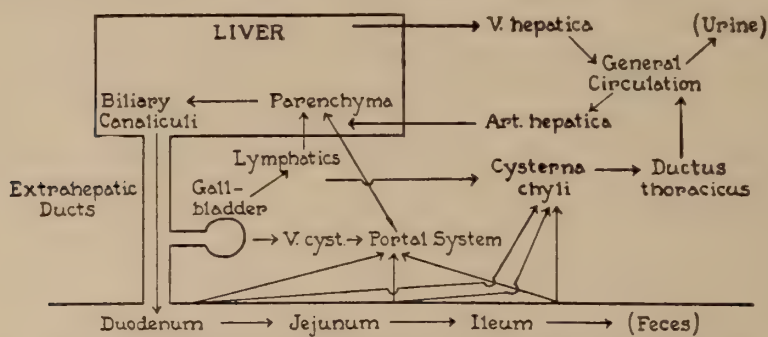


FIG. 2. Entero-hepatic circulation of bile (from Sobotka, H.: *Physiological Chemistry of the Bile*, Baltimore, Williams & Wilkins, 1937).

bile is concentrated about five times, and its pH becomes more acid (pH = 6 to 5), while sodium is lost in the form of carbonate by diffusion through the gall bladder wall. It was shown by Ottenberg and Kahn (14) in our laboratory that it is practically impossible to influence the pH of the bile by dietary measures, because of its very efficient buffering mechanism. The bile flow in a normal adult is between 1000 and 1500 cc. of liver bile in 24 hours. Animal experiments indicate that approximately one-seventh of the bile acids excreted into the intestine are lost through the feces, and a simple consideration shows that the maintenance of an even bile flow requires the production of that same amount every day. When all the bile is permanently withdrawn through an outside fistula, the liver can be induced to produce much more than under normal conditions with the entero-hepatic bile flow intact. I cannot go into the details of the recovery of the bile acids from the intestine, but the diagram indicates that the lymph flow participates in this circulation (fig. 2). The complementary

effect of biliary and pancreatic secretion upon the digestion and resorption of fats is too well established to require discussion. The influence of bile acids on the resorption of deficiency factors, such as vitamin A and its precursor, carotene; vitamin D (calciferol) and its precursor, ergosterol; of tocopherol (vitamin E) and other lipoid factors, such as the unsaturated fatty acids cooperating in the vitamin B complex, are also affected by the bile flow.

So much for the bile acids and their biological rôle, about which we are relatively well informed. In the case of the various steroid hormones, we know much about the physiological and pathological pictures caused by their absence and by their administration in various forms, by various routes and in various quantities. But here our knowledge ends, and we cannot go beyond vague conjectures why these substances, which are so similar to each other in chemical structure and physical properties, so specifically affect the primary and secondary sex organs, the integument and other organs and tissues.

Our knowledge is similarly limited in the case of the vitamins D, a group of substances derived from animal as well as plant sterols by irradiation. Here again, physiological and pathological observation is far ahead of a chemical explanation for the influence of this group of bone metabolism. The same holds for the related powerful synthetic derivative, dihydro-tachysterol, known as "AT 10."

I come now to the last part of this lecture. I said before that this diagram (fig. 1) was to serve two purposes. First it served as a table of contents, but now I wish to use it to illustrate the biogenetic interrelation between these steroids. The following facts stand out. The animal organism is able to synthesize the steroid skeleton without recourse to the ingestion of plant steroids. This has been proved by numerous ingenious animal experiments, for instance, by Schoenheimer (15) in studies of the cholesterol balance of the laying hen.

Chemical considerations indicate that the structure of the steroids, like that of the carotenoids, can be traced to C_5 units of the isoprene type. An alternative theory advanced by Reichstein assumes C_3 units of carbohydrate type. The synthesis of the steroid skeleton from small units has been confirmed by experiments with deuterium. The controversy concerning the ultimate groups used in this synthesis, while not acute at present, is not without importance, since the isoprene structure may be biogenetically related to the essential amino acid, leucine; in other words, "Are steroids ultimately synthesized in the wake of protein metabolism or of carbohydrate metabolism?"

On the basis of the conception that ontogenetic development duplicates phylogenetic development, important clues concerning the steroids may be expected from Comparative Biochemistry. Phytosterols make their appearance in monocellular organisms. The sterols found in lower animals

resemble phytosterols in structure and may be of alimentary origin; cholesterol found in invertebrates may likewise be alimentary and due to carnivorous habits. Synthesis of cholesterol becomes a certainty only in the vertebrates. Here, except for the lower types of fish, the bile acids make their appearance, hand in hand with the emergence of a calcified skeleton, with the requirement of vitamin D, the development of the parathyroid gland, etc. It is most likely that steroid hormones are absent in the invertebrates, that is, in animals which seem to be unable to synthesize the higher steroids.

I cannot at this occasion discuss the evidence offered by structural chemistry for the interrelationship of the steroids, but three points stand out which deserve mention. (a) I refuse the paradoxical assumption that the complicated steroid nucleus is synthesized independently in a dozen places like the various endocrine glands, because this seems incongruous with the remarkable economy of nature in other fields of chemical synthesis. (b) The so-called steric configuration of the skeleton is practically identical for all steroids known, or to be more accurate, of 256 structural possibilities, only two are realized by nature. (Special interest attaches to the shift in constellation in one center of asymmetry, which is responsible for the levo-rotation of cholesterol, whereas the bile acids are dextro-rotatory. Chemical events around the asymmetric carbon atom give us important clues regarding the intermediary substances in steroid metabolism, such as cholestenone, substances which may be of great biological importance and whose existence was first postulated and experimentally approached by Rosenheim (16).)

(c) Granting the biogenetic interrelation of the steroids, one would naturally assume a gradual degradation in the clockwise sense on the diagram rather than a stepwise synthesis the other way around. First, the amounts occurring in the animal body decrease in the clockwise sense, and the amounts of these potent hormones become smaller and smaller in nature, just as the yields decrease gradually in their industrial preparation from higher sterols. Second, the type of reactions leading from cholesterol to the male hormones consists of a stepwise degradation of the long side chain, following known reaction patterns. After the complete shedding of the long side chain, the removal of an angular methyl group makes possible stepwise removal of hydrogen from the nucleus, yielding one or two benzene rings in the female sex hormones.

At the end of the cycle we have inserted the carcinogenic hydrocarbons. When the structure of the most potent carcinogenic hydrocarbon that can be isolated from coal tar or laboriously synthesized *in vitro* became known, the similarity with the fundamental structure of the steroids was evident. Cook (17) remarked that "the same proliferation which characterizes the oestrous state is in some respects reminiscent of the early stages of malignant growth." A genetic relationship between oestrogens and carcinogens

in addition to the actual observed overlapping of their effects--seems not impossible, since further desaturation along the lines mentioned may lead from oestrogens to carcinogens. However, in this laboratory Dr. Edith Bloch worked up more than 3000 liters of urine from cancer patients without detecting any hydrocarbons of this type (18). It would be premature to pass judgment on the importance of carcinogenic hydrocarbons for the spontaneous tumors in man.

I do not wish to miss the occasion to refer to the work of the Russian chemist, Blagovestchenski (19). From numerous examples in the field of plant chemistry, he concludes that the formation of cyclic compounds, such as terpenes, alkaloids and steroids, is a sign of phylogenetic aging. As we have emphasized before the cyclic structure and the resulting stability of the steroid skeleton, a connection suggests itself between the cyclic nature of the steroid carcinogens and their ability to induce cancer, a disease of older age.

Chemistry and physics, on the one hand, have considerably advanced the knowledge of the steroids in recent years, and the isolation of biologically active steroid substances has been perfected to a marvellous degree. On the other hand, clinical medicine and physiology have utilized these substances with great advantage in diagnosis and especially in therapy in the gynecological as well as the general endocrinological practice. There still remains a gap between the empirical application of the steroids and our structural knowledge. An important help in bridging this gap is the study of disease involving the steroids. The belief that the investigation of the normal should precede that of the pathological has been called erroneous by an author who continues,

"As a matter of fact, the investigation of the abnormal in scientific research precedes that of the normal. The investigation of the abnormal is one of the most potent instruments for new discoveries. The method of experimentation, the most powerful tool of modern science, is in fact the creation of artificial conditions, in other words, the effecting of abnormal states" (20).

Thus, we expect that the clinical and experimental study of diseases will lead to the gradual unraveling of the biological problems in which the steroids are involved, and that in turn a fundamental understanding of this amazing group of substances will contribute to the perennial progress of diagnosis and therapy.

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THE ESTROGENS¹

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The subject of the estrogens has been presented so frequently and in such detail during the past few years, and again in the past months (1) that the majority of you should be familiar with many of its aspects. Therefore I take for granted that you will be more interested in phases which usually are not featured or discussed.

The estrogens are general growth substances which in the course of evolution have become more and more specialized in their function until their receptive organs finally are restricted mainly to the genital tract, considered in its broadest sense. This includes the breasts, the secondary sex characters, as well as the psyche, in addition to the actual genital tubes. Estrogenic effects may be obtained from lipoids derived from innumerable sources such as extracts of bacteria (2), yeast (3) and plants (4). In the lower plants, estrogens are obtained from any portion. In the phanerogams, or flowering plants, these lipoids are concentrated in the ovaries. Thus, even before the animal kingdom is reached, greater quantities of estrogen are found in the organs of sex, in contrast to the general soma.

Estrogens have been demonstrated in the ovaries of sea urchin, holothurian, crustacea (5), fishes (6), and snakes (7), likewise in the egg of the hen (6). The sex organs of some of these lower forms, including those of oviparous species, certain snakes and lizards (8), react to the sex hormones. In viviparous animals, even before the placentates are reached, a new organ is noted in the ovary. Following ovulation, the emptied ovisac rapidly changes into the corpus luteum. This bright colored and striking object early attracted attention of investigators (9). The dual function of the corpus luteum was unknown to the earlier biologists and misled them, as at that time they possessed no tests which distinguished between its two hormonal products, the estrogens and progestin.

On reaching the placentates, another organ, a special pregnancy gland, the placenta, is encountered, a yolk-placenta is present already in some viviparous snakes and lizards (10). The placenta acts not only as a middleman in conveying food to the fetus and returning waste products to the mother, but has developed a hormonal secretory function by which it

¹ Delivered at The Blumenthal Auditorium of The Mount Sinai Hospital as part of A Series of Lectures on the Steroid Hormones, April 7, 1941.

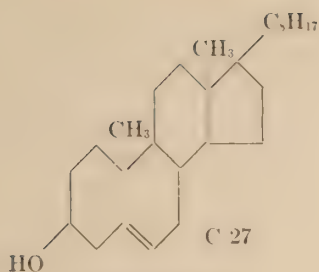
manufactures gonadotropic (11), estrogenic (12) and progestational hormones (13). Thus the pregnant uterus becomes an independent and autonomous shelter for the fetus, not only producing its own hormones, but also, as is seen in transverse myelitis, functioning when freed of central nervous control.

The name given to these lipid hormones which I am discussing tonight, is not unqualifiedly a happy one. The nomenclature is based upon a single action, namely the production of estrus in laboratory animals, but as the physician deals solely with *homo sapiens*, the highest of the primates who have no demonstrable estrus, it has seemed to me that the name that I originally proposed, that of "female sex hormone" would have been the better one, for many qualities not included in the name of "estrogen," such as the production of feminineness, including body configuration, the obvious feminine secondary sex characters such as breast development, hair distribution, voice and psyche, as well as the local effects upon the tubular sex organs and the control of the first part of the sex cycle are dependent upon this group of hormones. It is only the last-mentioned action which is covered by the present appellation.

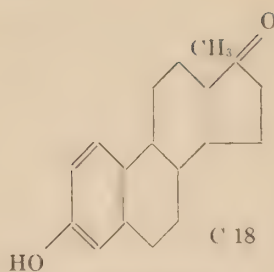
As preceding speakers in this symposium have pointed out, a close structural relationship exists between the almost universally present cholesterol, found throughout the body, and all the steroid hormones, embracing female and male sex hormones and adrenal cortical hormones. At first we were inclined to consider their physiological activity strictly associated with the common cyclopentenophenanthrene skeleton. It has since been found that far simpler bodies, for example, the two-ringed synthetic substance, "stilbestrol" (14), possesses estrogenic properties. Moreover, the specificity of the sex hormones themselves, among which we must include the adrenal cortical hormones, is not absolute. These latter possess varying degrees of estrogenic, androgenic and progestational powers (15, 16) which may play a rôle, at least in certain conditions of disease. This lack of strict specificity is further illustrated by the discovery that when the ovary is transplanted to a site of lower temperature (the ear of the rabbit), its secretion assumes androgenic properties; on retransplantation to the warmer abdominal cavity, estrogenic function is resumed (17).

Some antagonistic action exists between estrogens and androgens. To effect such antagonism or neutralization, excessive doses (far above physiologic levels) are required (18).

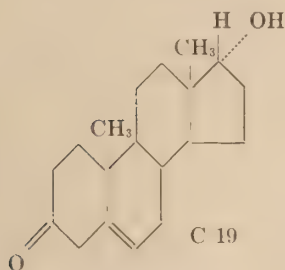
I shall omit the tests, both bioassay and chemical colorimetric, by means of which we recognize the presence and the strength of the estrogens, and by means of which we quantitate their occurrence in the secretions as in the blood, and the tissues—and in the excretions, as in the urine and feces. However, let me warn you that the data so far available are purely preliminary and tentative. They will require revision when more accurate methods are at our disposal. In spite of this, we may accept certain facts



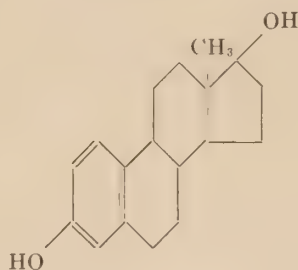
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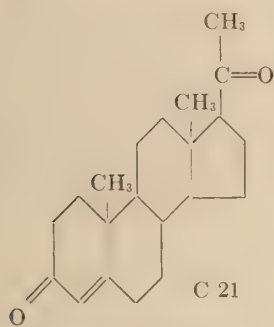
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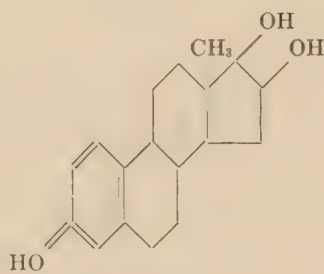
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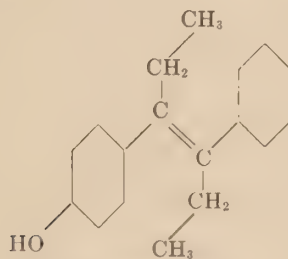
ESTRADIOL



PROGESTERONE



ESTRIOL



STILBESTROL

FIG. 1. Structural formulae of cholesterol and the steroid hormones. All have in common the cyclopenteno-phenanthrene nucleus. Below is shown the strong synthetic estrogen "Stilbestrol" as depicted by Dodds.

as demonstrated, namely that there is a striking contrast between the male and female, although both sexes have male and female hormones in their circulation and both sexes excrete these hormones in the urine and feces (19). In the male, small daily fluctuations occur, but the excretion on the whole appears to be constant. As yet, nothing conclusive can be said of the androgen contents of the blood for the tests for the male hormone are not sufficiently delicate. In the female, a regular estrogenic cycle takes place, with periodic fluctuation in the blood and excretions (20). This ebb and rise offers an explanation for the current theory of menstruation, the periodic menstrual bleeding characteristic of primates. As long as a certain level of blood estrogen is maintained, the activated uterine mucosa remains intact. When this level has been maintained and then when the estrogen falls below this concentration, irrespective of whether this is due to cessation of secretion, excessive destruction or increased excretion, uterine

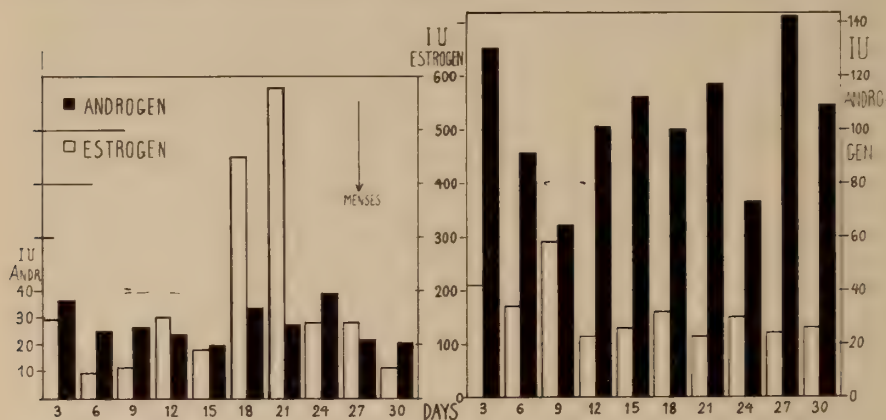


FIG. 2. Urinary excretion of estrogen and androgen during 30 days (bioassay). Left: Normal menstruating female. Right: Normal adult male.

bleeding supervenes (21). The rôle of progesterone in the complex phenomenon of menstruation will be discussed by another of the speakers.

In the human female, there is a short abortive menstrual cycle, averaging twenty-eight days, which is marked by a continued rise of estrogen in the blood until the time of menstruation is reached; then there is an abrupt drop coincident with the onset of the flow. The urinary excretion shows two peaks, corresponding approximately to the time of ovulation or of the ripening of follicles, the second reaching its acme some three to five days premenstrually.

When pregnancy takes place there is the long, fertile pregnancy cycle of two hundred eighty days, during which the blood estrogen shows a progressive increase from the second month onward, with an abrupt drop following upon the onset of labor. The increase in excretion is very marked, showing fluctuation but without regular peaks. This increased excretory level

likewise ceases at labor. Limitations of time prevent discussion of all the interesting topics concerning the variation in type of estrogens found—free, combined, etc.

Toward term, as much as 10,000 International Units of free estrogen constantly are found in the six liters of blood within the circulation, com-

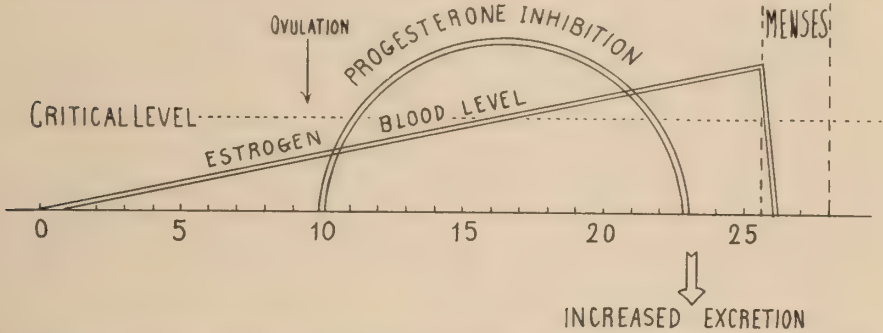


FIG. 3. Current theory of the menstrual cycle. Critical level in the blood must be attained to sensitize the uterine mucosa. A drop below this level is followed by bleeding. If estrogen alone is acting, the bleeding occurs after 10 to 15 days; if estrogen and progesterone together have produced the sensitization, withdrawal is followed by bleeding within 2 to 4 days.

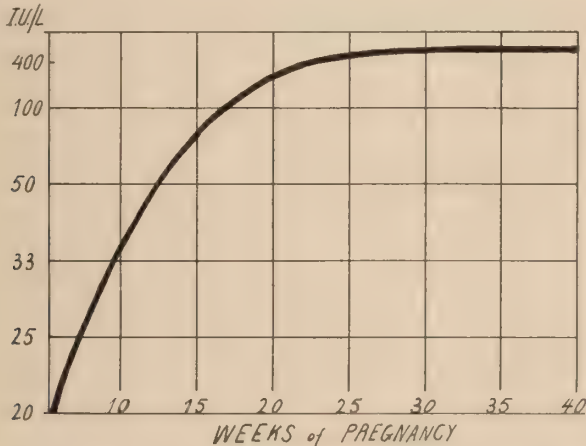


FIG. 4. Graph showing concentration of estrogen in circulating blood during the different weeks of pregnancy. The graph shows estrogenic activity expressed in international units of estrone per liter of blood.

pared to only 150 International Units, which is the highest amount reached in the normal, non-pregnant women, an increase of sixty-six times. The excretion in the urine during the short, twenty-eight day cycle, equals 1500 ± 300 International Units of estrone; in the long, 280 day pregnancy cycle, 7.5 to 8 million International Units or approximately 30,000 I.U. daily (22).

The continuous saturation of the female organism with estrogens throughout pregnancy produces characteristic changes in the genital system and breasts, which we associate with gestation. The uterus increases in length from 8 cm. to 36 cm.; its weight rises from 50 gms. to 1 kilogram; its musculature hypertrophies; its vascular supply augments immeasurably. Systemic changes which need not be taken up in this connection, likewise ensue. These changes result in great part from estrogenic stimuli.

The hormonal conditions associated with functional disturbances of the female genital tract have been presented so often that they require but passing mention. These disturbances include under and overfunction of the ovaries (23). Apparently in most instances the ovary is not the primary site of disturbance. The tendency at present is to ascribe the primary cause to the hypophysis. This question will not be settled until the, as yet little understood, intermediate metabolism of the sex hormones has been fully clarified (24) and until such non-hormonal factors as the effect of the state of nutrition—inanition, (25) obesity, etc., are more fully understood.

Certain important facts should be emphasized. By the use of the heart-lung-liver preparation (26) as well as by the simpler method of subjecting estrogens to the action of liver brei (27), it becomes apparent that liver tissue rapidly destroys estrogens when they reach this organ, either through the portal circulation or less directly, through the general vascular system. If 2000 International Units of estrogen are injected into the ear vein of the rabbit, they disappear from the circulation within one-half hour. That they are destroyed and not merely stored is shown by the fact that if then the entire rabbit is extracted and hydrolyzed to liberate combined estrogen, no activity can be demonstrated (28). This metabolic action of the liver has recently been suggested as the basis of a test for liver function (29). In Laënnec's cirrhosis of the liver, gynecomastia appears in a number of patients, as a rule only after ascites has developed. Provisionally the explanation must rest upon diminished liver function, in consequence of which the estrogens normally produced in the male are not destroyed, therefore, accumulate in excess and then activate the breasts. However, the coincident testicular atrophy also must be taken into account, although this *per se* is unaccompanied by gynecomastia (30). Other means of destruction or inactivation, doubtless, exist. For example, among those plants investigated, hyacinths cause disappearance of estrogens (31).

Notwithstanding that the estrogens are employed so universally and recklessly in clinical medicine, their pharmacology is in a state of confusion. To me it seems fortunate that these substances are almost water insoluble and, therefore, do not lend themselves readily to intravenous injection. In aqueous, alkaline solution and well buffered, they cause a slight, transient general peripheral vasodilatation (32) but exert little permanent effect on the blood pressure. On reaching the liver, as just mentioned, they

are rapidly destroyed or combined. Hence continuous secretion must necessarily occur to maintain a given blood level.

Certain other systemic effects are known. Castration produces concentration of blood; estrogens restore the blood volume to normal (33). Calcification appears to be increased by the estrogens (34). Large continued doses reduce growth rate (35), an effect which presumably explains the slowing up or cessation of growth noted at puberty. This may well be due to inhibition of the growth factor of the prepituitary rather than by any direct action. Yet my attempts to arrest adolescent gigantism by enormous doses of estrogens have proved futile.

The well known interaction between various endocrine glands and their dependence upon the function of other glands of this system, have in part been analyzed. Due to the effect of estrogens, recognizable changes in the adrenal cortex may develop (36); their functional significance is uncertain. The thymus is said to involute in response to estrogens (37).

There are other still less clearly understood mutual relations between the gonads and the thyroid (38), and pancreas (39). The reports are as yet too inconclusive and contradictory to warrant more than passing mention.

Prolonged administration of estrogens reacts upon the adenohypophysis, with resulting diminution of the secretion of the gonadotropic factor (40). In the sex cycle this same mechanism largely explains the alternate increase and decrease in gonadotropic secretion, which in turn periodically stimulates the ovaries. We utilize this same effect in the therapy of the menopause during which an excess secretion of gonadotropic factors is one of the main findings (41). Whether the numerous other pituitary factors are likewise influenced is not yet fully determined. Eventually excess effect on the hypophysis may cause this gland to increase to tumor proportions, as demonstrated experimentally (42). Repeated pregnancy stimulation, in rare instances, has caused homonymous hemianopsia due to pressure on the optic tracts by an enlarged hypophysis.

The ovaries respond to prolonged injection of estrogens by regressive changes which fortunately are not permanent (36). Otherwise many women who have as yet not borne children and who, therefore, have been dubbed as "sterile," actually would have been sterilized by ill-advised estrogenic therapy.

The local effects are apparent mainly in the pelvis and the breasts. The uterine effect manifests itself sequentially first by early and persistent vasodilatation (in thirty minutes) (43) as well as by an increase of the water content in this organ (in five to six hours) (44). Somewhat later the local hydrops is replaced by more permanent endometrial and myometrial changes, which physiologically are associated with the follicular phase of the sex cycle—vascularization, endometrial and myometrial hyperplasia.

The organs directly affected by the estrogens—I shall call them receptors for short—are the tubular genital tract, (the Müllerian ducts, Fallopian

tubes, uterus, vagina and also vulva), the breasts, and if undeveloped, as in prepuberty and infantilism, the secondary sex characters. The local effects vary somewhat, dependent upon the structure and function of these diverse organs. Nevertheless the response shows several main similarities—epithelial stimulation with mitoses, glandular acinic proliferation, hyperplasia of connective tissue and unstriated muscle. The oxygen consumption of the uterus increases above its initial resting level (up to sixty per cent augmentation) (45). The musculature subsequently undergoes definite changes in the character and rate of its contraction (45). These effects play a dominant rôle both in the sex cycle and in disturbances

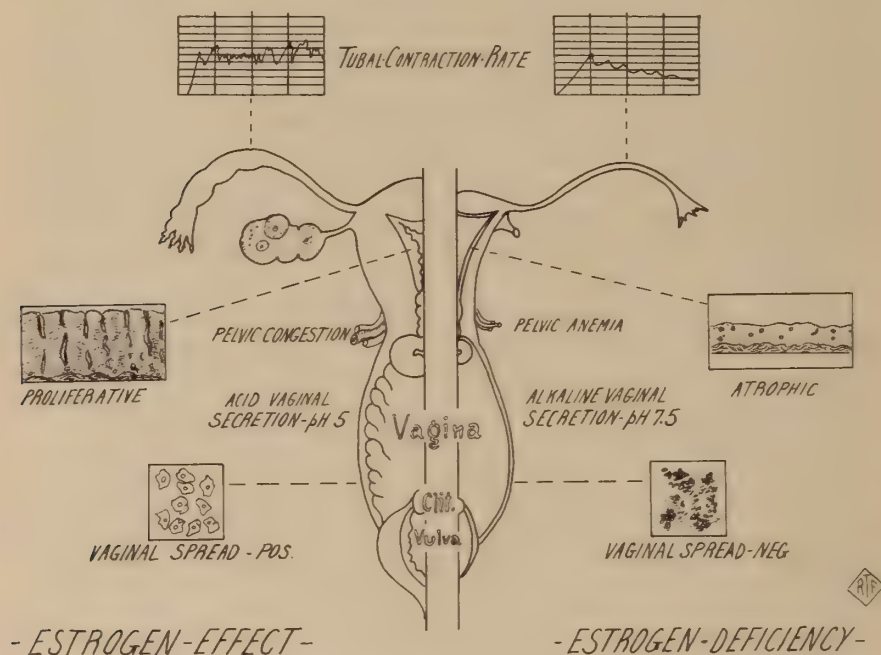


FIG. 5. Schema of estrogenic effect on female genital tract. Left: Estrogenic effect. Right: Estrogen deficiency.

arising from functional causes or consequent to our crude methods of therapy. Thus blocking of the ovum during its descent through the Fallopian tube may ensue (46) or loosening of the early impregnated ovum from its site of nidation in the uterus may result. The pelvic circulation is greatly influenced by the estrogens. It responds by arterial dilatation, capillary fullness, venous engorgement and lymphatic turgescence. Another distant effect is upon the nasal mucosa in the so-called "genital area" which becomes turgescence (47). Most striking are the tremendous changes resulting from prolonged estrogen saturation as noted in pregnancy, conditions of vascularity, familiar to every gynecologist and obstetri-

cian. In contrast, the intestine, skeletal muscles and spleen remain unaffected (45).

In view of the almost universal distribution of estrogens, existing both now and during the geological ages (for estrogens can be obtained from asphalt (48) formed many millenia ago) it is somewhat puzzling to note that both qualitatively and quantitatively the response of different species has remained so variable and unpredictable. Apparently size and body weight play but a minor rôle. Even among allied groups such as the rodents, sensitivity of response as well as differences of tissue reaction are encountered. For example, I may quote the finding that both in the guinea pig and in the pocket gopher, estrogens produce a marked relaxation of the symphysis pubis (49). In the guinea pig, intraperitoneal injection of estrogen causes the widespread formation of myofibromata in the genital

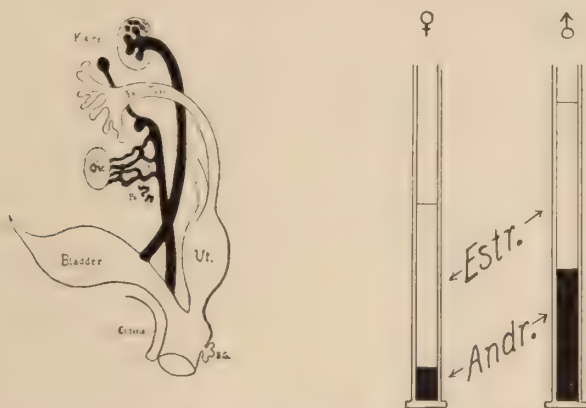


FIG. 6. Physiologic bisexuality in female and male. Fetal: Four month female fetus. Müller's Ducts in outline. Wolffian Ducts in black. Chemical adult: Urinary excretion of estrogens and androgens in both sexes.

tract as well as in other portions of the peritoneal cavity (50). In some species, the estrogens exert a carcinogenic action. This is best illustrated by the production of breast adenocarcinoma and cervical carcinoma in otherwise unsusceptible strains of mice. This subject will be discussed by another speaker.

It has long been known that sex is neither a static nor irreversible condition. Both in animals and in humans, hermaphroditism and intersexes occur. Masculinization of females and feminization of males have been observed and their causation traced to tumors. The subject has aroused increasing interest since it has become known that a *chemical* hermaphroditism (more precisely, a bisexuality) is a normal, universal occurrence in both sexes of human beings (51).

A crude attempt to evaluate the ratio of androgens and estrogens in both sexes has been made (52). This ratio as observed, is as yet so inexact that

only well marked deviations can be recognized (53). The hope appears warranted that smaller changes may become evaluable and that eventually these may explain the causation of such ill-defined syndromes as functional sterility, total alopecia, hirsutism, nymphomania and homosexuality, if the latter is founded upon a physical basis.

Already we are able to gage the hormonal changes present in femininization of the male, due to chorionepithelioma of the testis, for example. Such patients show the hormonal status normally noted in pregnancy—

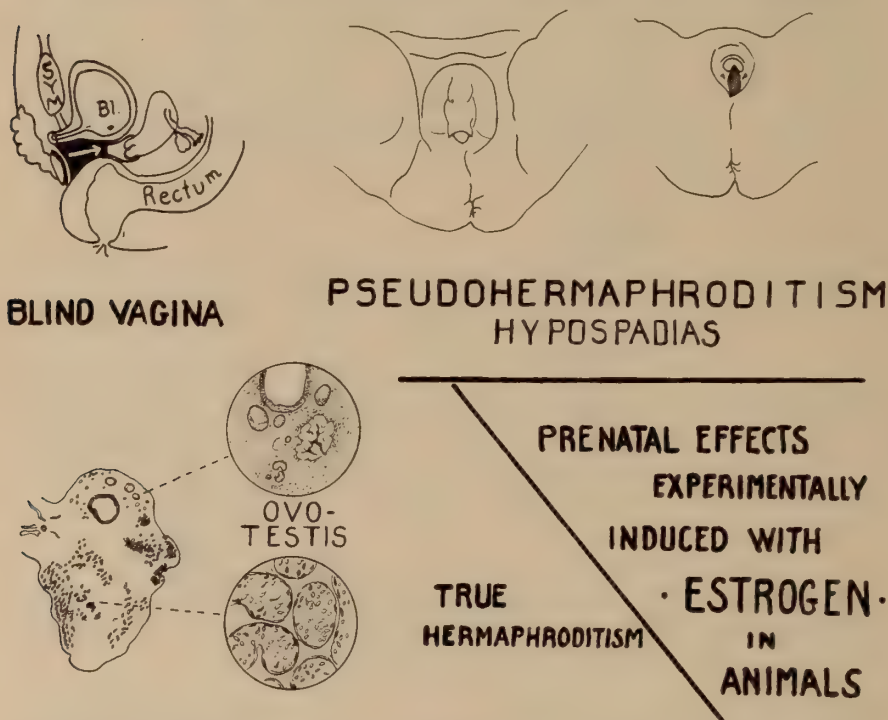


FIG. 7. Some of the more common genital malformations noted in human females. These can be produced in experimental animals with estrogens given in the fetal or neonatal period.

positive pregnancy test, increase of estrogens in the blood and urine. Masculinization of the female with hirsutism, bass voice, change of build and features due to arrhenoblastoma of the ovary, shows an increased production of androgen by the male tumor cells. Less accurately analyzable are the hormonal changes occurring in adrenal cortical carcinoma producing the adrenocortical syndrome. The symptoms appear to be of bisexual nature due to a great increase of both androgen and estrogen, and probably as well to the presence of new, non-physiological hormonal steroids (54).

Injection prenatally into the mother or fetus (55), or into the pouch

young of the opossum (56) demonstrates that some of the commoner genital malformations may be produced experimentally by estrogen or androgen. These include intersexes (ovo-testis) (57), if the gonads are affected, and hyperdevelopment of the sex organs of the opposite sex (uterus, prostate), also blind vagina, hypertrophy of the phallus, hypospadias, etc. (58).

The clinician is most keenly interested in therapy. As soon as new discoveries are announced, his first reaction is to ascertain whether these *nova* have practical applicability. In the past, more often than in the present, empiric therapy outstripped accurate, well grounded pharmacology and therapeutics. Not infrequently this hit or miss tendency has resulted in the production of unnecessary suffering, harm, and disillusion; occasionally it has led to brilliant results.

The estrogens have been widely used in almost every conceivable ailment that woman is heir to. In order to conserve time, I present a list of the functional disturbances and diseases for which these steroids have been recommended. I have tried them—reluctantly, I will confess, but out of a sense of duty—in a majority of these conditions. Where italicized I have found them effective.

THE SUGGESTED USE FOR ESTROGENS

THOSE ITALICIZED ARE ADVOCATED

General

Froehlich's syndrome	Migraine
Infantilism	Hypertension
Gigantism	Hirsutes

Prepuberty

Prematurity of newborn
Vulvovaginitis—gonorrhoeal

Puberty

Delayed puberty	Menorrhagia
Amenorrhea	Metrorrhagia
Oligomenorrhea	Acne
Dysmenorrhea	Hirsutes

Adult

Amenorrhea	Chronic cystic mastitis
Oligomenorrhea	Menorrhagia
Dysmenorrhea	Metrorrhagia
Sterility	Alopecia
Painful breasts	Hirsutism
	Toxemia of pregnancy

Climacteric

Preclimacteric neuro-vascular syndrome, menstruation persisting		
Menopause	<i>Neurovascular</i>	<i>Local atrophies</i>
	<i>Arthritic</i>	<i>Psychic</i>
	<i>Digestive</i>	Leucoplakia
		Kraurosis vulvae

In my opinion, the applicability of estrogens is limited to the following diseases.

Gonorrhea of infants and prepuberal adolescents, as an aid to chemotherapy (59). It effects keratinization of the vulva and vagina. The gonococcus cannot exist upon such epithelium.

Menopause. Relief of the neurovascular, digestive, arthritic and local atrophic symptoms of the menopause (60).

The estrogens available for therapeutic use are *Estrone*, *Estradiol*, and *Estriol*. Each, weight for weight, has a different potency. These lipoids are absorbable by many routes—by mouth (larger doses required); parenterally by subcutaneous injection; by inunction; by implantation; and vaginally, in the form of suppositories. With due allowance for the portal of entry, of the chemical nature of the estrogens, and of the dosage, the effect is identical. Therefore, except when local effects for gonorrhea of children or for senile vaginitis are desired, for both of which I employ vaginal suppositories of estrone, I use and recommend the oral exhibition of alpha estradiol, in tablet form. In the menopause, thirty tablets, each containing 1/2 mg. of alpha estradiol, are prescribed in the following way: 1 tablet, 3 times a day for 4 days; 1 tablet, 2 times a day for 5 days; 1 tablet once a day for 5 days; and 1 tablet every other day for 3 doses. The therapy is then intermitted until the flushes reappear. During this interval, it is advantageous to give small doses of phenobarbital, $\frac{1}{4}$ of a grain, one to three times a day. As soon as the flushes reappear, another course is given. Every effort should be made to increase the time intervening between courses until finally therapy may be discontinued.

To some of you, the limits of estrogenic therapy which I have set may appear absurdly rigid. Nevertheless they are based upon trial, experience and reflection, and in my opinion, are fully valid. To me the present excesses appear as unwarranted, as if you attempted to treat these same diseases with insulin or parathormone. The triumph obtained in the therapy of diabetes by insulin is no more clearcut or decisive than the victory over the incapacitating disturbances of the menopause. Menopause disturbances, although they do not directly imperil life, are far more widespread and numerous than diabetes, and because of this, play a role of even greater communal importance.

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VITAMIN THERAPY IN RAYNAUD'S DISEASE PRELIMINARY REPORT

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Definition. Raynaud's disease is characterized by attacks of vasospasm of the extremities and occasionally of the tip of the nose and of the earlobes, manifested in the sequence of pallor, cyanosis, and redness, and precipitated by exposure to cold. There is no demonstrable block of the large arteries of the limb, and ulcerations and phlyctenules,¹ when present, are limited to the skin involved in vasospasm. The condition may be associated with sclerodactyly. Raynaud's disease is an entity by itself to be distinguished from the vasospasm involving the digits which may occur secondarily in obstructive vascular disease of the extremities.

Classically it occurs most frequently in females between adolescence and middle age. The specific temperature precipitating an attack of vascular spasm varies somewhat from patient to patient, but is usually within a narrow range between 40 and 55°F., above and below which attacks may not occur. Less frequently, a patient may have spasm on returning to a warm environment from the critical range of low temperature. Secondary factors modify the response—humidity, warm clothing, unusual fatigue, imbibition of cold or hot liquids (1). Emotional stress or pain will seldom elicit an attack unless the extremities are exposed to a temperature near the critical range for spasm.

Pathology. In advanced cases that have progressed to organic changes in the affected tissues, the histologic findings are: 1) arteritis, characterized by intimal thickening, atrophy and fibrosis of the media, and perivascular cellular infiltration; 2) fibrosis of the corium with atrophy of the skin appendages; 3) decalcification and resorption of the bones of the terminal phalanges. In cases of moderate severity arteritis alone is present. However, no organic lesions have been reported in the simple type of vasospasm (2).

Studies of the capillary loops in the nailfolds during the course of spasm have shown segments of abnormal dilatation and contraction (3).

Etiology. Four different concepts of the causation of the disease have been suggested up to the present, the two most widely held being those of Raynaud and of Lewis.

1) In 1862, on the basis of clinical observations of the six patients who

¹ Phlyctenules: A term used to indicate "minute gangrene" without surface breakdown.

rigidly fulfilled his own diagnostic criteria, Raynaud stated: "Local asphyxia of the extremities ought to be considered a neurosis, characterized by enormous exaggeration of the excitomotor energy of the gray parts of the spinal cord which control the vasomotor innervation" (4). (The term "neurosis" was not then used in its modern psychologic sense.)

2) Lewis made clinical experiments in patients to study the temperature responses of the digital vessels and was particularly impressed with the persistence of the original vasospasm after sympathectomy. He concluded in 1929 that the primary cause of spasm of the digital vessels in Raynaud's disease of the common type is not an abnormal nervous impulse, but a local fault of the vessels (5).

A modification of the above theories was suggested by Allen and Brown (4) in 1932, on the basis of their clinical study of 147 cases of the simple uncomplicated spasmodic type of the disease. They accepted Raynaud's theory as the principle conception, also admitting the occurrence of a "local fault" as an added factor in advanced cases. However, they stress the viewpoint "that the disease is ordinarily an equivalent of psychoneurosis or neurasthenia."

3) In 1932 Bernheim and London (14) suggested that inadequate calcium intake may be associated with heightened irritability especially involving the digital vessels and is expressed in sensitivity to cold. Bernheim and Garlock (6), in 1935, suggested that the complicating sclerodactyly was brought about by hyperactivity of the parathyroids which, in turn, was induced by the depletion of bone calcium. Recently, however, they withdrew the latter hypothesis (7).

4) Chronic arsenical intoxication has also been considered an etiologic factor (8).

Standard Therapy. The various therapeutic procedures generally employed are based on the above conceptions of the etiology of the disease.

1) Sympathectomy, to interrupt the flow of impulses from the central nervous system into peripheral vasoconstrictor fibers, has been performed by Adson and Brown, Smithwick (9), and Telford (10). Cure of symptoms of Raynaud's disease of the lower extremities has been reported after lumbar sympathectomies. Objectionable side-actions have occasionally occurred, however, such as constipation, priapism or impotence. In sharp contrast to the excellent results after lumbar sympathectomy, the clinical results after cervicodorsal sympathectomy have been unsatisfactory. The vascular spasms of the fingers have been either only temporarily relieved or not at all. The reasons for the discrepancy are varied. Technically, the isolation of these sympathetic ganglia and preganglionic fibers is difficult. The operation may be incomplete because of the necessity for conservation of the brachial plexus into which the first thoracic nerve passes. In instances in which the operative procedure itself has been complete there has been demonstrable regeneration of the vasoconstrictor fibers. Further-

more, when regeneration has not occurred, it has been suggested that the vessels of the upper extremities are rendered more sensitive to circulating epinephrine after ganglionectomy. There is some dispute, however, concerning the truth of this statement (11). It has also been suggested that the vessels of the lower extremities are under more marked central nervous control, removal of which, therefore, is much more likely to relieve vasospasm, whereas the vessels of the upper extremities are less dependent on vasoconstrictor regulation and are, therefore, subject more particularly to the "local fault."

2) Mecholyt iontophoresis of the extremities to induce vasodilatation by stimulating the vagus has been without significant therapeutic effect (12).

3) Histamine iontophoresis to induce capillary dilatation given in conjunction with papaverine hydrochloride by mouth has been reported as helpful in several cases (13).

4) Bernheim and London (14) reported the successful treatment of four cases of vasospasm of the extremities, which were interpreted as atypical borderline types of Raynaud's disease, by means of "a high calcium regimen, with viosterol, orange juice, and tomato juice as adjuvants."²

Based on the theory of a disordered calcium metabolism, parathyroidectomy has been performed as treatment for Raynaud's disease with scleroderma (6, 7).

5) Because of the observation that spontaneous and permanent remissions of Raynaud's syndrome have occurred during pregnancy, estrogens were administered in several cases, but without effect (Silbert (15)). One case was reported in 1936, however, of apparently successful treatment with estrogenic substance (16).

CASE REPORT

History. In February, 1940, a houseworker, aged twenty-six, came under observation with Raynaud's syndrome involving the hands and feet during the preceding two years. Within that time she had had pneumonia complicated by empyema, but had recovered completely.

On the taking of a detailed dietary history a striking deficiency was found, requiring immediate correction during consideration of therapy for Raynaud's disease. Her diet had consisted essentially of rye bread and coffee three times a day, and occasional broth or meat.

Examination. She presented cold, moist, cyanotic extremities. She also had slight pretibial pitting edema for which no circulatory cause could be ascertained, fissures at the angles of the mouth, erythematous papules about the eyes, and severe periodontoclasia. Her basal metabolic rate was plus 25 per cent, but there were no other clinical evidences of hyperthyroidism.

Course. The cheilitis, both on clinical and dietary grounds, suggested riboflavin

² Therapy consisted essentially of adding 1 qt. of milk per day; viosterol, 30 drops; tomato juice, 16 oz.; orange juice, 8 oz.; and lactose, $\frac{1}{2}$ oz. to the patient's diet. The vitamin content of the supplement as estimated by current standards is: A—7560 I.U.; B₁—400 I.U.; B₂—560 S.B. units; C—325 mg.; nicotinic acid—trace. (See table III for minimal daily requirements.)

deficiency and the edema suggested hypoproteinemia and vitamin B deficiency. She was, therefore, given a multiple vitamin capsule³ (group I) before each meal, and was put on a balanced diet. This regimen was begun February 10, 1940. In ten days her hands no longer blanched in cold water in laundering, but became reddened promptly. On re-examination February 29, 1940, the periocular and labial lesions had disappeared, and spasms were not demonstrable when her hands were placed in water of 40 to 50°F. She remained asymptomatic throughout the subsequent cold weather. (For subsequent history, see Case 4, tables I and IV.)

The experience with this patient suggested the need for studies of dietary, and especially of vitamin, intake in patients with Raynaud's syndrome. Twenty-one patients with this disease were studied. The data on these patients form the basis of this preliminary report.

As indicated in table I, eighteen patients were females and three were males. The age range was between twenty and forty-eight years. The duration of symptoms before the beginning of treatment varied from one month (Case 20) to twenty years. One patient, not listed in the chart, had had typical spasms for the past forty years, beginning at the age of twenty-two. The age of onset varied from thirteen years to the middle forties.

Sixteen patients presented only typical, uncomplicated vasospasm. Three patients (Case 1, 12, 18) also had scleroderma and sclerodactyly. One patient with vasospasm (Case 11) had phlyctenules of the fingertips without ulceration. Case 19 had an associated polyarthritides. The clinical severity was not dependent on the duration of the disease. The attacks of spasm lasted from several minutes to three-quarters of an hour.

Eleven patients had received previous treatment. The only therapy which had been successful was lumbar sympathectomy which had been performed on two patients (Cases 3 and 6). Cervicothoracic sympathectomy on two patients (Cases 6 and 11) had been ineffective. Parathyroidectomy, periarterial stripping, high calcium diet, typhoid injections, thyroid gland administration, histaminase and histamine injections, mecholyl iontophoresis, had been tried without effect.

Several clinical facts of interest were determined. All complained of fatigue and lassitude of the type frequently called "neurasthenic." Two patients, without scleroderma, had low basal metabolic rates, minus 20 per cent and 25 per cent (Cases 13 and 15), for which thyroid gland had been given in large doses without improvement in the lassitude, the vasospasm, or the metabolic rate itself. Two patients had elevated rates, plus 25 per cent and plus 26 per cent (Cases 4 and 17) without clinical findings of hyperthyroidism.

The highest environmental temperature at which symptoms were noted varied with individual patients but in general it was approximately 55°F. Three patients, however, had attacks of spasm at about 70°F. One patient, (Case 11) had attacks in summer heat if a slight breeze blew

³ For composition see table IV.

TABLE I

CASE	SEX	AGE	OCCUPATION	AGE AT ONSET	TYPE OF SYNDROME	HIGHEST ENVIRONMENTAL TEMPERATURE AT WHICH SPASMS OCCUR	BASAL METABOLISM RATE	PREVIOUS TREATMENT
1. H. G.	F	40	Housewife	21	Spasms, hands, feet, tip of nose, earlobes, <i>early scleroderma</i>		+1	Histamine and histamine injections—no change
2. E. S.	F	26	Secretary	23	Spasms, hands, feet	45		0
3. R. G.	F	46	Housewife	26	Spasms, hands, feet	65	-10	Lumbar sympathectomy—feet asymptomatic
4. H. L.	F	28	House-worker	26	Spasms, hands, feet	50	+25	0
5. R. B.	F	42	Housewife	14	Spasms, hands, feet	60		0
6. F. B.	F	30	Secretary	17	Spasms, hands, feet	65		'28—typhoid injection—no change '29—upper sympathectomy—improved 1 month '30—lumbar sympathectomy—feet well '31—periarterial stripping, right brachial—no change '34—high calcium diet—no change '39—histamine—no change
7. E. M.	F	27	Seamstress	13	Spasms, hands, feet	60		0
8. M. G.	F	43	Seamstress	40	Spasms, hands, feet	45		0
9. M. d'A.	F	34	Secretary	19 30	Extreme cyanosis Spasms, hands, feet	60		High calcium diet—no change
10. R. Bo.	F	45	Housewife	44	Spasms, hands, feet	55		Estrogens—no change
11. A. G.	F	42	Housewife	30	Fissuring of fingertips, bed-ridden because of general debility	Any breeze even at 90 induces a spasm		'30—high calcium diet—no change '34—parathyroidectomy—no change '37—right dorsal sympathectomy—improved for few months '38—left dorsal sympathectomy—improved for few months
12. D. C.	F	43	Housewife	30	Spasms, hands, feet; <i>early scleroderma and sclerodactyly</i>	75		Histamine and histamine injections—no change

TABLE I—*Concluded*

CASE	SEX	AGE	OCCUPATION	AGE AT ONSET	TYPE OF SYNDROME	HIGHEST ENVIRONMENTAL TEMPERATURE AT WHICH SPASMS OCCUR	BASAL METABOLISM RATE	PREVIOUS TREATMENT
13. F. Bi.	F	39	Housewife	32	Spasms, hands, and feet	65	-20	Thyroid gland—gr. iv—no change
14. F. H.	F	26	Writer	24	Spasms, hands, and feet	65	Normal	0
15. P. B.	F	20	Milliner	17	Infrequent spasms, generally burning red hands	60	-25	Thyroid gland—gr. iii—no change
16. T. P.	F	48	Housewife	42	Spasms, hands, and feet	60		
17. A. M.	M	20	Barber	18	Spasms, hands, and feet	50	+25	Histamine and histaminase injections—no change
18. W. K.	M	23	Machinist	20	Spasms, hands, and feet; phlyctenules of fingertips; scleroderma, face, axillae	70	Normal	Mecholyl iontophoresis—no change
19. F. S.	M	47	Day laborer	38	Spasms, hands, and feet, paresthesias, face, lips. Polyarthrititis	70		0
20. S. F.	F	47	Seamstress	38	Spasms, hands	75		0
21. S. B.	F	48	Housewife	43	Spasms, hands	65	Normal	Mecholyl iontophoresis—no change. Saline injections—no change

on her hands. In many patients a difference was noted between the two hands in skin temperature and in their sensitivity to cold.

A complete physical and neurological examination was made at the beginning of treatment. One patient (Case 16) had essential hypertension. Case 6 had mitral stenosis and insufficiency and had had one episode of cardiac insufficiency. All of the patients had damp, cool, slightly cyanotic hands and feet at normal room temperature (about 70°F.), even in the absence of vasospasm. Although many patients complained of tingling in their digits, which awakened some of them during the night, none had altered vibration or tactile sensation.

Pre-treatment Dietary Findings. All of the patients kept diet diaries, most of which were completely reliable. Because of limitations of space, the detailed record of only one patient and a chart of the total daily intake

of calories and units of vitamins of all the patients are presented (tables II and III). The minimal daily requirements, according to present standards, which are still tentative, are indicated in table III.

Although some of the patients had a fair caloric intake, only three had an adequate intake of vitamin C; only one had a borderline intake of vitamin A; and only one, a borderline intake of vitamin B₁ and B₂. All of the others had a low intake of all the vitamins except of nicotinic acid. Whether or not this type of diet is frequent in a comparable control group of patients without symptoms of Raynaud's syndrome remains to be determined. The group of patients studied was heterogeneous economically and educationally, with choice of diet directed by ignorance, fads, or indifference, as well as by poverty.

Some of the patients had additional clinical findings of vitamin deficiency, which were proved such by their favorable response to therapy. The following were noted:

Case 1. Cheilitis, small ulcerations on buccal mucosa, tenderness at tip of tongue and intolerance to sweet and sharp-tasting foods.

Case 4. Cheilitis.

Case 10. Cheilitis.

Case 17. Cheilitis.

Case 20. Cheilitis and hypersensitivity of the tip of the tongue.

Case 21. Cheilitis and paresthesias of the face and tongue.

One patient, Case 5, had presenile incipient cataracts.

Immediate Results of High Vitamin Therapy. The form of therapy employed in these patients underwent modifications and is still being changed during continued observation. The composition of the capsules given is indicated in table IV. One group of patients received a multiple preparation of vitamins, "Group I", before each meal, without change in their dietary habits (Cases 1, 4, 12, 15, 16, 17, and 20) (table V).

All except Cases 16 and 19 stated that they improved in their sense of well-being after about a week of treatment. After about two weeks they reported that their extremities were subjectively warmer and more comfortable. Some reported this change within the first week. The extremities appeared pink and warm on examination and the dampness gradually diminished. The time required for the lessening or disappearance of the attacks of vasospasm varied with different patients.

Qualitatively, the vasospasm after treatment was begun involved a shorter length of the digits and could be provoked only at lower temperatures than previously, and was also of shorter duration. As improvement progressed, the white stage disappeared, and the attack consisted only in a brief cyanotic stage followed by redness. The next change was the omission of the cyanotic phase as well and the induction of only the red phase on exposure to cold. The improvement was first apparent in the proximal segment of the digits subject to spasms.

TABLE II
Diet for one week—Case 2

12 7 40	12/10/40
2 cups coffee	1 cup coffee
1 jelly doughnut	1 jelly doughnut
chow mein	baked Virginia ham
1 cup coffee	2 slices white bread
	green peas
1 cup coffee	fried sweet potatoes
walnut strudel	coffee
stuffed fish	coffee and cake
German grits	2 eggs fried
1 cup coffee	2 slices rye toast
	cake and coffee
12/8/40	cake and coffee
2 eggs fried	
2 English muffins, toasted	12/11/40
2 cups coffee	$\frac{1}{2}$ glass milk
relish cheese	1 cup coffee
1 cut poppyseed strudel	1 jelly doughnut
1 cup coffee	ham and cheese sandwich—rye
shrimps, scallops, smelts, clams	1 cup coffee
filet of sole	coffee and cake
julienne potatoes	sliced tongue salad
lemon meringue pie	2 slices rye bread
1 cup coffee	2 parkerhouse rolls
$\frac{1}{2}$ chicken salad sandwich	1 cup coffee
1 cup coffee	
cookies	12/12/40
12/9/40	2 glasses milk
1 glass milk	1 cup coffee
1 $\frac{1}{2}$ cups coffee	1 jelly doughnut
1 jelly doughnut	Spanish omelet
2 cuts meat—pot roast	coleslaw
1 fruit muffin	French fried potatoes
1 slice white bread	white toast
1 cup coffee	coffee
1 cup coffee and walnut strudel	12/13/40
1 sardine sandwich—rye toast	$\frac{1}{2}$ glass milk
1 cheese sandwich—rye toast	1 cup coffee
coffee and cake	jelly doughnut
English muffin and marmalade	ham and cheese on white toast
coffee and candy	potato salad
	coffee
	No dinner
	2 Scotch and sodas
	coffee and cake
	candy, potato chips, nuts, pretzels

In an attempt to identify the vitamin or vitamins of therapeutic importance in Raynaud's disease, whole vitamin B complex, either alone, or as a fortification of the total vitamin therapy was then given. The doses varied from six to twenty capsules per day for a period of several weeks.

TABLE III
Average daily diet based on week's food intake

CASE NO.	TOTAL CALORIES	CARBOHYDRATE, CALORIES	PROTEIN, CALORIES	FAT, CALORIES	B-1 (THIAMIN, INTERN. UNITS)	B-2 (RIBOFLAVIN, SHERMAN BOURQUIN UNITS)	C (ASCORBIC ACID)	A (INTERN. UNITS)	NICOTINIC ACID	CALCIUM
1. H. G.	700	400	140	160	170	290	800	2,000	Borderline	Low
2. E. S.	1,588	849	279	456	267	298	211	1,440	Borderline	Low
3. R. G.	1,446	669	269	283	281	273	1,005	2,610	Good	Low
4. H. L.	1,020	630	200	190	250	310	1,250	3,000	Borderline	Low
5. R. B.	895	341	230	324	235	310	900	2,500	Borderline	Low
6. F. B.	1,006	629	195	182	259	309	1,262	3,100	Good	Low
7. E. M.	860	552	174	134	254	440	1,550	3,200	Good	Low
8. M. G.	800	525	145	130	250	300	850	2,400	Borderline	Low
9. M. d'A.	1,271	771	221	240	261	318	1,901	5,053	Good	Low
10. R. B.	650	385	135	130	180	240	850	2,000	Borderline	Low
11. A. G.	643	380	132	121	175	236	810	2,106	Borderline	Low
12. D. C.	710	405	145	160	150	240	1,000	2,100	Borderline	Low
13. F. B.	910	410	135	365	200	300	1,500	2,000	Good	Low
14. F. H.	877	240	185	452	237	374	5,750	1,588	Good	Borderline (0.6 gm.)
15. P. B.	1,000	620	200	180	260	310	1,250	3,000	Borderline	Low
16. T. P.	867	408	137	322	169	294	2,200	721	Borderline	Low
17. A. M.	766	522	144	100	54	40	500	1,200	Borderline	Low
18. W. K.	1,440	645	272	525	281	459	1,080	2,883	Good	Borderline (0.6 gm.)
19. F. S.	581	317	95	183	80	189	458	1,200	Borderline	Low
20. Changed diet immediately before beginning of observation										
21. S. B.	886	339	224	323	232	311	900	2,420	Good	Low
<i>Minimal daily requirements—sedentary adult (20, 21, 22, 23)</i>										
	2,000		240		390-495*	900*	1,560	5,000	12-15 mg.*	0.8 gm.

* Vary with caloric intake, especially carbohydrate.

Requirements of Pantothenic Acid and Pyridoxin unknown.

All of the patients, except Case 1, received vitamin B complex.⁴ Cases 2, 5, 8, 10, 13, 14, and 21 were given only vitamin B complex at one prolonged stage of treatment. Clinical improvement in these patients was

⁴ Table IV.

essentially the same as in the group receiving "Group I."¹ The most favorable clinical response appeared with six to nine capsules per day. Patients given the contents of twenty capsules in an elixir did not respond any more quickly.

In the group treated intensively with vitamin B complex, Cases 9 and 11 had a recurrence of spasm after a period of improvement, although the hands between attacks were dry and of normal pink color in contrast to the damp, cool, cyanotic condition previously. The general sense of well-

TABLE IV
Composition of vitamin products used

<i>Vi-Syneral Special Capsule, designated "Group I" in Chart</i>	
Thiamin—2 mg.	Derived from yeast and fortified with synthetic material.
Riboflavin—1 mg.	
Pyridoxin—1 mg.	
Nicotinamide—10 mg.	
A—8,000 I.U.	Concentrate from fish liver oil.
D—1,140 I.U.	
C— 500 I.U.	
E—2 minims wheat germ oil	
Ca —50 mg.	
P —40 mg.	
Fe —14 mg.	
Cu — 1½ mg.	
Mn— 1 mg.	
Mg— 1 mg.	
Zn — 1 mg.	
I — .15 mg.	
<i>Lederle vitamin B Complex capsule</i>	
Thiamin—1 mg.	Derived from liver.
Riboflavin—¼ mg.	
Pyridoxin—130 micrograms	
Filtrate factor—12 rat growth units or 50 chick dermatitis units	
Nicotinic acid—2 mg.	

being was maintained. That this recurrence of spasm, in spite of other indications of improvement, may have been due to overtreatment is suggested by the fact that the spasm again cleared up when high vitamin therapy was terminated and the patients were temporarily maintained on merely a prescribed normal diet.

It was next attempted to determine whether any one specific component of the vitamin B complex was the essential factor in the improvement of symptoms of Raynaud's syndrome, or whether a specific ratio among the components of the vitamin B complex was necessary.

TABLE V
Summary of therapy

NAME	SEQUENCE OF THERAPY	DOSAGE	RESULT	REMARKS
1. H. G.	"Group I"	3 per day	3 plus	No longer under observation. In New Orleans
2. E. S.	B complex Adequate diet	6 per day—3 weeks 4 per day—2 weeks Since Feb. '41	4 plus Asymptomatic	
3. R. G.	B complex and also "Group I"	20 per day in elixir for 2 weeks 1 per day	2 plus	
	B complex and "Group I"	10 per day in elixir 3 per day for 2 weeks	2 plus	
	"Group I" and adequate diet	3 per day—1 month	2 plus	
4. H. L.	"Group I"	3 per day—2 weeks Feb. '40	4 plus	Discontinued medication, poor diet. Recurrence of symp- toms in Oct. 1940
	"Group I" and B complex	2 per day—Feb. '41 9 per day	4 plus	Has had 6 to 9 capsules of B complex daily. Optimum is 9 capsules. Diet is low in B still
5. R. B.	B complex	6 per day—4 weeks	2 plus	Dropped from treatment after 2 months as she refused to change diet
6. F. B.	B complex	6 per day—4 weeks 9 per day—4 weeks	4 plus 4 plus	
	Thiamin chloride	20 mg. per day —2 weeks	Slight regression	
	B complex and "Group I"	6 per day 1 per day	4 plus	
	Riboflavin	6-9 mg. per day	Slight regression	
	B complex and adequate diet	6 per day	4 plus	
7. E. M.	"Group I" and B complex Adequate diet	1 per day) 6 per day) 3 months	2 weeks 4 plus Asymptomatic	
8. M. G.	B complex "Group I" Adequate diet	6 per day—3 weeks 3 per day—1 month 3 months	4 plus 4 plus Asymptomatic	
9. M. d'A.	B complex	9 capsules per day for 2 weeks	4 plus	Improved in 1 week
	Thiamin chloride	20 mg. per day— 1 week	Marked regression	
	B complex	9 to 12 per day for 2 months	4 plus	Improvement noted in 2 weeks. No difference in response to either 9 or 12 capsules
	Riboflavin, "Group I"	3 to 6 mg. per day; 2 per day for 2 weeks	Slight regression	
	B complex, ade- quate diet	6 per day	4 plus	Improved in 2 weeks
	Adequate diet		Slight regression	
	B complex, ade- quate diet	4 per day	4 plus	

TABLE V—Continued

NAME	SEQUENCE OF THERAPY	DOSAGE	RESULT	REMARKS
10. R. Bo.	B complex "Group I" Riboflavin B complex	6 per day 3 per day 9 mg. per day 6 per day	4 plus 4 plus Slight regression 4 plus	Allergic to liver
11. A. G.	Nicotinic acid B complex Adequate diet only "Group I"	50 mg. before going out into cold—about 3 per day 9 per day—2 months 3 per day	Transient relief in cold but no prolonged effect 4 plus then 3 plus Slight regression, but improved over original status 3 plus	At beginning of therapy, intolerant of a breeze even on a hot day—typical spasms. With prolonged B complex treatment had occasional spasms after 3 weeks of being asymptomatic. Then given adequate diet only
12. D. C.	"Group I" B complex "Group I" and B complex	3 per day 6 per day 1 per day 3 per day	1 plus 1 plus 1 plus	
13. F. B.	B complex "Group I" and adequate diet	15 per day—2 weeks; then 6 per day—1 month 3 per day	1 plus 1 plus	
14. F. H.	B complex Thiamin chloride B complex B complex in elixir	8 per day—3 weeks 20 mg.—4 days 9 per day—18 days 30 per day—1 week	3 plus Severe regression Slight change No improvement	Improvement noted in 17 days Overdosage? Discontinued observation in 6 weeks
15. P. B.	"Group I" Riboflavin Adequate diet, "Group I"	3 per day—3 weeks 6 mg. per day 2 per day	1 plus No change 2 plus	Very early case. Spasms are infrequent. Generally has striking erythema and burning sensation of hands
16. T. P.	"Group I" B complex B complex, adequate diet	6 per day—1 month 6 per day—2 months 6 per day—2 months	1 plus 1 plus 1 plus	Blood Pressure 210/100
17. A. M.	Group I B complex	3 per day—1 month 6 per day—1 month	2 plus 4 plus	Uncooperative concerning diet. Stopped coming as soon as improved
18. W. K.	B complex in elixir B complex, Group I Riboflavin Pyridoxin, adequate diet Group I	20 per day—5 days 9 per day—4 weeks 3 per day 6 mg. per day 10 to 50 mg. per day—10 days 3 per day for 3 weeks	2 plus 2 plus No further change Marked regression 1 plus	Raynaud's and moderate scleroderma. Ulceration of fingertips Fingers blue and cold at temperature of 80°F. Condition worse than at beginning of any therapy

TABLE V—*Concluded*

NAME	SEQUENCE OF THERAPY	DOSAGE	RESULT	REMARKS
19. F. S.	B complex Riboflavin Pyridoxin "Group I," B complex	9 per day 6 mg. per day 30 mg. per day 1 per day 6 per day } 3 weeks	2 plus Slight regression Marked regression 1 plus	Polyarthrititis Hands blue and cold on warm day Very recent change
20. S. F.	"Group I"	3 per day for 2 weeks 2 per day for 4 weeks	4 plus Asymptomatic	But under observation too recently
21. S. B.	Riboflavin B complex	9 mg. per day— 10 days 6 to 9 days for 6 weeks	No change 4 plus	Slight improvement in cheilitis which was present 4 years Continued improvement in cheilitis. Improvement in spasms in first 10 days

Response to Therapy—Code

1 plus—At critical temperatures, spasms are of shorter duration, less painful, though they occur almost as frequently. Extremities have become of normal color.

2 plus—Critical temperature has changed, spasms occur at lower temperatures than formerly, last much less, and are less frequent.

3 plus—As above, but spasms are very infrequent.

4 plus—Rare spasms, at intervals of several weeks in spite of the frequent occurrence of temperatures at which spasms may occur.

Asymptomatic—no spasms for a period of several months of observation with exposure to temperatures which normally elicited spasms.

Regression is indicated in the chart in words.

Thiamin chloride, 20 mg. daily, was given to two patients, Cases 9 and 14, who had become asymptomatic on whole vitamin B therapy after having had numerous attacks of spasm every day. After three days of thiamin administration there was a distinct setback. The thiamin chloride was discontinued and the vitamin B complex was used again. The response to the second course was distinctly slower, requiring in these patients ten days and three weeks respectively, in contrast to the initial three days and ten days.

Riboflavin, 6 to 9 mg. per day, was given to four patients, Cases 9, 10, 15, and 19, who had previously improved on vitamin B complex. There was a slight setback. They noted more cyanosis of the fingertips, although the original symptoms did not return. Case 10, who had cheilitis, was given riboflavin; the cheilitis improved completely within three days, but in that time the vascular spasm of her fingers and toes returned. When she was again given the vitamin B complex, the spasms ceased. Case 21, also with cheilitis, was given riboflavin first for ten days, with improvement in the labial lesion but without any change in the spasms. She was then given the vitamin B complex alone, 6 capsules daily, with prompt improvement in the spasms.

Because of a possible analogy between Raynaud's disease and the experimental pyridoxin deficiency known as rat acrodynia, pyridoxin was given in doses of 10 to 15 mg. daily to two patients, Cases 18 and 19, who had improved under whole vitamin therapy. Within two weeks they had completely regressed to their original severe condition in every respect. The setback with this fraction was particularly marked. These patients are now being treated again with the "Group I" capsules with some return of improvement.

Nicotinic acid, in doses of 50 mg., was given to one patient, Case 11, to be taken just before she went out into the cold. A generalized flush occurred immediately after each dose and prevented the occurrence of vasospasm. This was employed at the very beginning of her treatment, as she was the most miserable patient of all. There was no evidence of enduring effect. However, the result in this one case is insufficient for any well-founded opinion, and the subject will be investigated further.

In addition to the administration of vitamins, the dietary habits of the patients were changed to conform with standards of adequate intake of vitamins and minerals.

Late Results of Treatment. Following relief of symptoms on the high vitamin regimen, three patients who had had a moderate degree of vasospasm have been maintained on only a balanced diet for the ensuing three cool months, and another for one month of weather which formerly induced attacks. The period of improvement is too short for more complete evaluation.

Of the twenty-one cases treated from six weeks to one year, fifteen patients have shown varying degrees of relief from vascular spasm when treated with either total vitamins or with the vitamin B complex, as indicated in table V.⁵ Scleroderma was completely unaffected. Three patients, Cases 2, 7, and 8 are completely asymptomatic at present. Patients who had cheilitis did not give a different response from that of the others. The first patient to be treated, Case 4, became asymptomatic, but with return to her habitually inadequate diet and cessation of treatment she had a recurrence. Improvement again resulted after resumption of therapy.

DISCUSSION

Two interpretations of the significance of these results of high vitamin B therapy in Raynaud's syndrome may be considered—first, that vitamin deficiency is causally unrelated to the vascular disease although coincidental with it, the clinical improvement being a non-specific effect resulting from improvement in general health. Second, that a more intimate relationship exists between the two conditions, possibly superimposed upon a constitutional determinant for the disease. The incidence of multiple vitamin

⁵ One plus improvement is not included.

deficiency, as indicated by the presence of cheilitis, is greater in this series of patients than in general medical practice. The selectively beneficial results of treatment with the vitamin B complex also suggest such a relationship. At present, one may not go beyond indicating these two alternative explanations.

Assuming for the moment that the vitamin deficiency is of basic importance, one perceives several difficulties in its practical application in therapy. One of these is the incomplete state of knowledge of vitamin dosage, effects, synergisms and antagonisms. Another is the frequent incomplete reversibility of certain vitamin deficiencies once established, and the need for large maintenance dosage to prevent relapse, as Sydenstricker (18) reported in the treatment of pellagra. A third, is the possible hazard of overdosage. Finally, the degree of organic change in the blood vessels in Raynaud's disease may be reversible only to a limited extent.

SUMMARY AND CONCLUSIONS

The dietary history and clinical findings in a group of twenty-one patients with Raynaud's syndrome are reported which suggest that a vitamin deficiency is an important factor in its provocation. Twenty-one patients were treated for a period of six weeks to one year with either "total vitamins," or with vitamin B complex. Fifteen showed distinct relief from attacks of vascular spasm. Three are at present asymptomatic and are maintained on a normal diet alone. The vitamin B complex appeared to be the effective therapeutic group of vitamins.

Which, if any, specific factor is essential could not be determined. Thiamin chloride, riboflavin, pyridoxin, when used individually, were ineffective. Thiamin chloride and pyridoxin in large doses actually caused severe exacerbation of symptoms in patients who had previously improved under vitamin B complex therapy. It appears probable that the ratio between the several components of the vitamin B complex is important. The pathogenetic mechanism underlying the disease state, however, could not be determined in relation to the vitamin deficiency.

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AN INTRA-GROUP HEMOLYTIC TRANSFUSION REACTION DUE TO THE Rh AGGLUTINOGEN AS A RESULT OF ISO- IMMUNIZATION IN PREGNANCY

MAX D. MAYER, M.D., AND PETER VOGEL, M.D.

[From the Gynecological Service of Dr. S. H. Geist and the Laboratories of The Mount Sinai Hospital]

For a number of years there have been reported intra-group hemolytic transfusion reactions which could not be explained adequately. Most of these reactions have been described in women who had never received a previous blood transfusion but had recently been delivered or had had a spontaneous miscarriage (1 to 7).

Zacho (8) in 1936 was the first to describe an atypical agglutinin as the cause of the transfusion reaction in a woman who gave a history of having had four previous consecutive stillbirths and then had had a premature separation of the placenta following which a transfusion was given resulting in a typical transfusion accident. This he attributed to an atypical isoagglutinin which acted on the donor's cells. This particular agglutinin had the property of greater activity at 37°C. than at lower temperatures which was contrary to what ordinarily had been noted for atypical isoagglutinins. Zacho did not mention any relationship between the presence of the atypical agglutinin and the obstetrical history.

In the same year, Culbertson and Ratcliffe (6) described an intra-group transfusion reaction in a woman delivered by Cesarean section. They, also, found an atypical agglutinin in her blood which agglutinated 23 out of 24 group O donors when the centrifuge method of Landsteiner and Levine was used. Soon after they found another patient whose serum agglutinated 3 group O donors tested. The fourth donor (mother of the recipient) was found compatible. An uneventful transfusion was given. They noted that in both cases intra-group agglutinins were demonstrated during the puerperium.

It was not until 1939 that Levine and Stetson (9) gave some explanation for this phenomenon when they reported the case of a woman who delivered a macerated fetus. The husband being of the same blood group as the patient, group O, was used as the donor. A typical hemolytic transfusion reaction followed. They showed that an atypical agglutinin was present in the patient's serum. This agglutinin was more active at 37°C. and after a number of months disappeared from the blood. In testing numerous group O donors, approximately 80 per cent of the blood samples were agglutinated by this patient's serum.

Because of this evidence it was believed that this antibody developed as a result of immunization and it was suggested by Levine and Stetson that the products of the fetus served as an antigenic stimulus. Presumably the fetus inherited from the father a dominant agglutinin which was absent in the tissues of the mother, who was thus immunized.

Since Levine's original article there have been a number of such cases which have been reported (10 to 16). A number of similar transfusion reactions have occurred in patients who have had repeated transfusions and it has been shown that the agglutinin was induced as a result of the antigenic stimulus of the donor's blood (17, 18).

About a year ago Landsteiner and Wiener (19), after injecting rhesus monkey blood into rabbits, produced an anti-rhesus serum. Levine found in tests done jointly with Wiener (12) that the anti-Rh serum corresponded to the warm agglutinins which develop in some pregnant women and in certain patients who received repeated transfusions.

In testing a random population with anti-Rh serum it was found by Landsteiner and Wiener (20) that the red cells of approximately 85 per cent of the population, irrespective of the four blood groups and the factors M and N, are agglutinated by this serum, that is, they are Rh-positive. In 15 per cent of the population this factor is lacking; these people are Rh-negative.

An Rh negative woman, married to an Rh positive man, becomes sensitized to Rh positive blood by repeated pregnancies. A transfusion of Rh positive blood may then cause a reaction, due to the antibody that has been developed, even if the bloods are of the same group.

The following case is described to add additional evidence of the role of the Rh agglutinin as the causative factor in hemolytic reactions following transfusions of so-called homologous blood.

CASE REPORT

History (Adm. 469352). Mrs. G, 40 years old, was admitted to The Mount Sinai Hospital on February 17, 1941, to the service of Dr. Samuel H. Geist, with a history of vaginal bleeding for six weeks, and chills and fever for one day. She had had nine pregnancies, five of which terminated in miscarriage usually associated with chills and fever. She was a patient in this hospital in 1931, in 1933, and in 1939, in each instance for an infected abortion. The uterus was persistently retroflexed. On this, her fourth admission, she stated that her last normal period was three months ago. For two months she had had irregular bleeding, some fever, and abdominal pains.

Examination. The patient was thin, acutely ill, and moaning. There was slight cardiac enlargement and a systolic murmur was heard at the apex. Pelvic examination showed profuse bleeding and an enlarged uterus, sharply retroflexed. The temperature was 101.2°F., hemoglobin 68 per cent. The urine was negative.

Course. The uterus was replaced anteriorly; the temperature fell to normal; the bleeding became slight. On the fourth day following admission she suddenly aborted a three and a half months fetus and had a massive hemorrhage. She went into deep shock. The hemorrhage was controlled by immediately packing the uterus and an intravenous infusion was started followed by 500 cc. of bank blood, group O, cross-matched at room temperature, one day old. The blood pressure rose from 10 to 72

systolic and 50 diastolic. Three hours after transfusion she had a sudden severe chill and her temperature rose to 104.2°F. The blood pressure was now 110 systolic and 70 diastolic. In the operating room the packing was removed and it was found that the placenta had passed with it. There was no intra-uterine manipulation.

The patient then developed a marked oliguria with frank hematuria and hemoglobinuria. For the next two days the total output was only 130 cc. Icterus developed. At this time the hemoglobin had dropped to 31 per cent, white blood cells were 20,000 per cm. with 92 per cent polymorphonuclear leucocytes. Because of severe vomiting a Wangenstein tube was inserted and the patient given large doses of bicarbonate and a continuous infusion of Hartmann's solution; later one-sixth molar sodium lactate solution was substituted. The urea nitrogen was 70 mg. per cent; the carbon dioxide combining power 42.4 vol. per cent; total protein 3.8 gm.; cholesterol 180 mg. The patient's blood was checked, and found to be group O, Rh-negative, but no atypical agglutinins could be detected at this time. Her husband was found to be Rh-positive. The blood of the donor who gave her the reaction was also found to be group O, Rh-positive. She was now given 600 cc. of blood from an Rh-negative donor without any reaction. Fluids were forced to about 2500 cc. daily until edema appeared and the patient's heart developed a gallop rhythm. The daily output of urine averaged 50 cc. and vomiting continued. Digitalis was started. For five days her condition remained unchanged. She then received glucose and distilled water. On the seventh day she went into pulmonary edema for which she received atropine, aminophyllin, and tourniquets applied to the extremities. On the eighth day she finally began to void in amounts up to 300 to 400 cc. The urine was of fixed specific gravity of 1014 and the blood urea nitrogen remained at 70 mg. per cent. Eleven days after her first transfusion the patient had a sudden onset of right lower quadrant pain and a tender mass was felt there. This was diagnosed as a hemorrhage into the rectus sheath. The hemoglobin had risen to 48 per cent, and the patient was given a 500 cc. transfusion of Rh-negative blood, again without any reaction. From this point on there was steady improvement. The blood urea nitrogen fell to 58 mg. per cent on the fifteenth day and to 20 mg. per cent on the twentieth day after the transfusion reaction. The albuminuria disappeared and the hemoglobin rose to 60 per cent.

The mass in the right lower quadrant shrank progressively so that at the time of her discharge it was only a small fraction of its original size. The uterus was fairly involuted and retroflexed. The importance of contraception was explained to the patient.

COMMENT

No anti-Rh agglutinins could be demonstrated in the patient's blood immediately following the transfusion accident because of the absorption of this agglutinin by the donor's cells. Ten days later, however, the agglutinin was detected in her serum. The blood of the donor which caused the reaction showed distinct agglutination of the red cells with the patient's serum after standing in a water bath at 37°C. for fifteen minutes and then centrifuging the tubes. Agglutination also occurred with numerous group O, Rh-positive donors tested, but no clumping took place with several Rh-negative donors. The anti-Rh agglutinin could no longer be detected after the fifth week.

We have here a clear example of a type of severe intra-group transfusion reaction such as is seen in certain cases of repeated transfusions or transfusions in pregnant women. In this case the patient, lacking a cer-

tain factor in her blood which was present by heredity in her offspring, developed an antibody against the factor during her pregnancies. When she was transfused, because of her exsanguinating hemorrhage, the new blood happened to contain the factor against which she had developed the antibody.

It is characteristic that in pregnancy the intra-group hemolytic reactions usually occur following the first transfusion, in contrast, to the transfusion accidents which take place after repeated transfusions. It is most important that obstetricians and gynecologists should realize that such accidents are likely to occur during pregnancy. The Rh factor in the fetus is responsible for the iso-immunization in most cases, but other factors may also immunize (13). Careful compatibility tests at the appropriate temperature should be performed as suggested by Levine (21) and when necessary an Rh-negative donor procured.

It is also of importance to cross-match Rh-negative donors with patients who have anti-Rh agglutinins since occasionally there may be some differences in the specificity of the Rh (22). The original blood sample should always be saved; since, once a severe transfusion accident has taken place the circulating agglutinin may be entirely absorbed by the transfused red cells and then compatibility tests will not detect the agglutination which may be present.

It should be mentioned that this patient had five spontaneous miscarriages. Such a history is frequently found in women in whom transfusion accidents are reported (11, 12, 23). In addition a high percentage of babies with erythroblastosis fetalis are delivered of such mothers. The interesting correlation and possible genesis of this condition has been studied by various authors (23, 14, 24, 25). Careful obstetrical histories should be taken before transfusions are given.

SUMMARY

We report a history of five spontaneous miscarriages in a woman in whom a transfusion accident took place following transfusion of Rh-positive blood. The patient was found to be Rh-negative and anti-Rh agglutinins were demonstrated in her serum. She received two uneventful transfusions from Rh-negative donors and then made a complete recovery.

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LYMPHOSARCOMA OF THE STOMACH

HARRY YARNIS, M.D.

[From the Surgical Service of Dr. Ralph Colp]

One thousand and thirty-five cases of neoplasms of the stomach were diagnosed in The Mount Sinai Hospital from 1933 to 1940. Lymphosarcoma was the final diagnosis in twelve of these cases, an incidence of 1.2 per cent. It is important to differentiate this type of tumor from carcinoma because surgery offers a better prognosis in the early cases of the former and radiotherapy is definitely indicated in the advanced or inoperable cases. Clinically, it is impossible to make this diagnosis with certainty; however, in the following case the diagnosis of lymphosarcoma was suggested preoperatively.

CASE REPORT

History (Adm. 466414). A 62 year old unmarried nurse stated that six months prior to her admission to the hospital she had experienced sharp epigastric pain radiating to the back; this was somewhat relieved by belching. The pain was spasmodic and lasted several minutes; its recurrence was neither related to the intake of food nor was there relief after the intake of alkalis or food. Three weeks prior to admission the severity of the pain was markedly increased and three days before she entered the hospital she vomited about a pint of blood. There was no weakness or faintness after the hematemesis, but rather a definite sense of relief from her epigastric distress and pressure. Her appetite was poor and she had lost fifteen pounds since the onset of her illness. There were neither dysphagia, nausea nor other digestive disturbances. The past history was irrelevant; one sister had died of breast carcinoma.

Examination. When she entered the hospital, the examining physician noticed the characteristic *fetor oris* which is peculiar to persons who vomit blood, but there were no signs of active bleeding. The pulse rate was 90 per minute and the blood pressure was 144 systolic and 80 diastolic. The blood hemoglobin was 69 per cent and the red blood cell count was 3,700,000 cells per cu. mm. The physical examination was essentially negative. The abdomen was soft and no masses were palpated. The first stool in the hospital was normal in color and did not contain occult blood; since the site of the bleeding was near the cardia, it is probable that practically all of the blood was vomited. There was an absence of free hydrochloric acid in the fractional test meal, even after the hypodermic injection of histamine. The total acidity was 20. Blood was present in most specimens.

Roentgenologic examination of the stomach after the ingestion of a barium meal revealed the rugal markings to be spread apart as if by markedly hypertrophied rugae or by intruding masses. Below the cardia an ulcer was simulated but an actual ulcer crater could not be demonstrated (fig. 1). Peristalsis over the lower half of the stomach was sluggish but progressed to the antrum and the mucosal pattern here was not definitely abnormal. There was no retention of the barium meal at the six hour

observation. The roentgenologic examination suggested that the upper half of the stomach was distinctly abnormal and that this abnormal appearance was caused by either giant rugae or by tumors belonging to the group of lymphoblastoma (Dr. M. L. Sussman).

The stomach was then examined by means of the flexible gastroscope. Projecting from the lesser curvature into the lumen of the stomach and below the cardia, there were several grayish, necrotic masses of varying sizes. On the posterior wall of the body of the stomach and extending to the greater curvature, there were numerous small, sessile nodules covered by relatively normal mucosa. The entire picture did not look like a typical carcinoma and the gastroscopist considered the possibility of

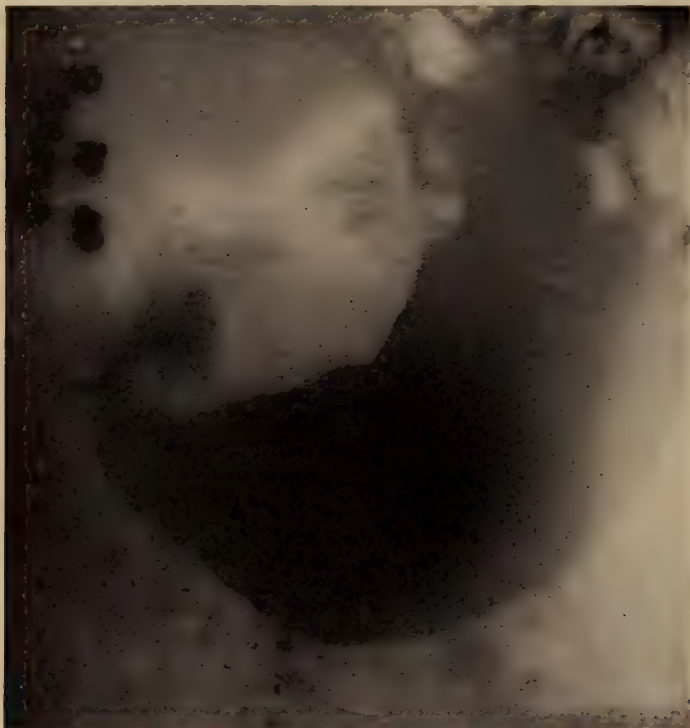


FIG. 1. Roentgenological examination of the stomach after the ingestion of a barium meal revealed the rugal markings to be spread apart as if by markedly hypertrophied rugae or by intruding masses. Below the cardia an ulcer was simulated but an actual ulcer crater could not be demonstrated.

a tumor arising from the submucosa of the stomach, probably a lymphosarcoma. From roentgenologic and gastroscopic appearances, it seemed that the mucosal distortions were due to infiltrations in the submucous layer of the stomach by tumors of the lymphoblastoma group.

Operation. Exploratory laparotomy was then performed. The stomach was normal in size and appearance. Palpation revealed no thickening or abnormality of the stomach wall. Gastrotomy was then performed in the cardiac region. Near the lesser curvature there were areas of necrosis. Nodular masses were felt on the mucosal aspect of the posterior wall. A biopsied specimen revealed fragments of polypoid gastric mucosa showing submucosal infiltration by tumor in one area, most

probably lymphosarcoma. Resection was not done because the lesion extended to the cardia and because this type of tumor frequently responds to radiation therapy.

COMMENT

Lymphosarcoma is rarely diagnosed pre-operatively. In this case, roentgenologic and gastroscopic studies suggested the diagnosis. Resection of the tumor should be performed if possible, since the disease remains localized to the stomach for a relatively long time. In the inoperable cases, radiotherapy has proven of definite value in relieving symptoms, prolonging life and, perhaps, effecting a permanent cure.

CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Wednesday, December 6, 1939

Huge Fibrosarcoma of the Pleura

[From the Surgical Service of Dr. Harold Neuhof]

History (Adm. 441686; P.M. 11200). A thirty year old woman was admitted to the hospital on June 8, 1939. Five and a half years before admission she noted sticking pain in the left chest associated with cough productive of small amounts of non-foul sputum. X-ray examinations carried out at that time revealed a large tumor in the upper portion of the left chest. Radiotherapy administered over a period of six weeks produced no change in the size of the lesion. She was observed carefully and during the next three years the tumor did not increase in size. During the subsequent two years, however, it became progressively larger, and an x-ray examination taken before admission revealed that the mass now occupied practically the entire left hemithorax. Three weeks before admission she experienced sharp pain over the left chest which persisted for several days. This pain was associated with severe dyspnea. In the course of the three weeks before admission these symptoms disappeared and she then entered the hospital for investigation of the tumor mass.

Examination. The patient was obese and well developed. The heart appeared displaced to the right. There was flatness over the upper left chest, anteriorly and posteriorly. Breath sounds and fremitus were diminished to absent over these areas. Faint râles were also heard in these areas. The blood pressure was 130 systolic and 80 diastolic. The impression was that of pleural tumor with effusion (fibroma or fibrosarcoma).

Laboratory Data. Blood: hemoglobin, 88 per cent (Sahli); white blood cells, 9,200 with a normal differential count. The blood chemistry findings were normal. The Wassermann reaction was negative. The urine and stool examinations were negative. An Ascheim-Zondek test of the urine was negative. The electrocardiogram revealed no significant abnormalities. X-ray examination of the chest revealed a mass in the upper thorax with areas of calcification within it. This was interpreted as being of mediastinal origin, and probably benign.

Course. Two hundred cubic centimeters of grossly bloody fluid were aspirated from the left chest. This clotted immediately. No tumor cells were found in the fluid. In order to determine whether this lesion was operable, a thoracoscopy was done after a preparatory pneumothorax. A well encapsulated vascular tumor was visualized. There was no evidence of metastases. A biopsy was considered too hazardous because of the vascularity of the tumor. It was assumed that the blood in the pleural cavity had come from a ruptured vessel from the surface of the tumor.

Surgical removal of the tumor was then attempted. The left lung was found to be collapsed, the remainder of the pleural cavity being filled with a large vascular tumor which was broadly attached to the posterior mediastinal paravertebral region. Attempts to remove the tumor were blocked by profuse bleeding. During the operation the patient went into profound collapse and died.

Necropsy Findings. There was a large tumor originating from the subpleural tissues in the posterior *mediastinum*, freely movable, and lying free in the left pleural cavity. The left *lung* was completely compressed, and posteriorly the tumor extended beyond the midline into the right chest. The neoplasm itself was enormous in size but displayed no infiltrative tendencies. Although there was no evidence of a hemorrhagic state of the tumor, there were several markedly dilated blood vessels on the surface. On section, it was very cellular, composed chiefly of fibroblasts.

Comment. *Dr. Klempner.* Because of the tremendous size attained by these tumors, they have been categorized as "giant tumors of the pleura." They are not very frequent in occurrence. These tumors are characterized by their bulk, their nodularity and marked cellularity. The latter is so predominant that one may classify the tumor as a fibrosarcoma of low grade malignancy.

Dr. Touroff. Experience has shown that the type of benign neoplasm represented by this case, follows one of two courses: 1) it may grow to such a large size as to be completely beyond any surgical aid; or 2) it may undergo malignant change. Therefore, all such cases should receive radiotherapy for a period of four to six weeks. If at the end of this time there is no response, x-ray treatment should be discontinued. The patient should then be subjected to exploratory thoracotomy. The procedure is comparatively safe. The present tendency is to explore the thorax as readily as the abdomen. The previous tendency, to hesitate about exploring the thorax, has been largely dispelled by improved methods of anesthesia and improved thoracic surgical technique.

Reported by *Abner Kurtin, M.D.*

Wednesday, December 20, 1939

Papillary Adenocarcinoma of Testis; Recurrence Six Years After Orchidectomy

[From the Medical Service of *Dr. George Baehr*]

History (Adm. 444739; P.M. 11265). This was the first admission of a forty-two year old German refugee, who complained of pain in the left thigh. His past history revealed that six years before admission a left orchidectomy had been performed for a sarcoma (?) of the testicle. Aside from a period of confinement in a concentration camp one year before admission, during which time he developed a transient swelling of the legs and hands, he was well until three weeks prior to admission. At that time, without any preceding trauma he developed severe pain in the left thigh, extending from the hip to the knee. The pain was unremitting, more

marked mesially, and appeared to be in the muscle rather than in the bone. About five hours later he was awakened by substernal oppression and precordial pain radiating to the left shoulder, which was accompanied by dyspnea and marked anxiety. A tentative diagnosis of myocardial infarction was made, but then discounted after three successive electrocardiograms proved to be normal. Two days later he developed a cough productive of bloody sputum. These symptoms disappeared within five days.

Examination. The patient was slow and guarded in his movements, always sparing his left lower extremity. He seemed quite exhausted. No lymph nodes were palpable. The trachea was in the midline. The lungs were clear throughout. The heart was not enlarged. The rhythm was regular, but tachycardia was present. The sounds were of fair quality. No murmurs were audible. The blood pressure was 130 systolic and 80 diastolic. A well healed appendectomy scar was present. The left testicle was missing. No abdominal viscera or masses were palpable. Rectal examination was negative. The left thigh was voluntarily flexed at the hip. Full extension was possible, but resulted in pain in the thigh. There was neither limitation of motion at the hip joint, nor any local bony tenderness. The straight leg-raising test caused pain. The reflexes were equal and active. The muscular and sensory status was negative.

Laboratory Data. Blood: hemoglobin, 100 per cent; white blood cells, 14,200 with 88 per cent polymorphonuclear neutrophils. Sedimentation time, 32 minutes. Wassermann reaction, negative. Urine and stool examinations, negative. A Friedman test of the urine was positive down to 10 cc.; smaller amounts of urine gave negative results. Electrocardiogram revealed prominent P waves. X-ray examination of the pelvis, lumbosacral spine and proximal half of each femur did not reveal any bony abnormalities. Chest x-ray examination showed both lungs to be studded with innumerable submiliary nodules, suggesting a metastatic neoplasm. Vital capacity was 2500 cc. Ether time, 5 seconds.

Course. The temperature was essentially sub-febrile throughout. It appeared obvious that this man was suffering from a metastatic neoplasm. The history of orchidectomy for tumor, plus the positive Friedman test, pointed to a recurrence of the testicular malignancy. The orthopedic consultant pointed out that the x-ray examination of the hip did not indicate a diagnosis of metastatic neoplasm, that traction had improved motion at the joint, and that by now rectal examination suggested retroperitoneal lymph node metastases. Hence, even though it was suspected that there was metastatic hip-joint involvement, it seemed more logical to apply radiotherapy to the retroperitoneal tissues. This was done but the clinical course persisted in a down-hill fashion. Several episodes of chest pain occurred, accompanied by bloody sputum. At one time a loud friction rub developed in the lower right axilla. Fluoroscopy of the chest showed a tremendous increase in the size of the nodules in the lung, almost replacing the normal pulmonary parenchyma. A hard mass became palpable on the lateral wall of the left pelvis. The patient's respirations became more and more labored, apparently a result of marked reduction of pulmonary capacity. He died four weeks after admission and eight weeks after the onset of symptoms, with a picture of marked dyspnea and air hunger.

Necropsy Findings. There was a large, retroperitoneal tumor mass on the left side of the abdominal cavity wherein vessels were embedded. These included the hypogastric artery and vein. The latter vessel was filled with a tumor thrombus which extended up into the inferior vena cava. The tumor was very cellular and

showed extensive necroses. The *lungs* were filled with metastatic nodules, varying in size from that of a pea to that of a cherry, and many of these bulged through the pleura. The *heart* vessels were remarkably free of coronary sclerosis. One small metastasis to the myocardium was present. Microscopically, the tumor was a papillary adenocarcinoma.

Comment. Dr. Klemperer. The pathological findings are quite typical of all tumors that grow into veins and metastasize via the blood stream. This is most often seen in neoplasms of the kidney, adrenal, and testis, and is characterized by massive pulmonary metastases, and relative absence of involvement of the liver, spleen and bone. These conditions existed here.

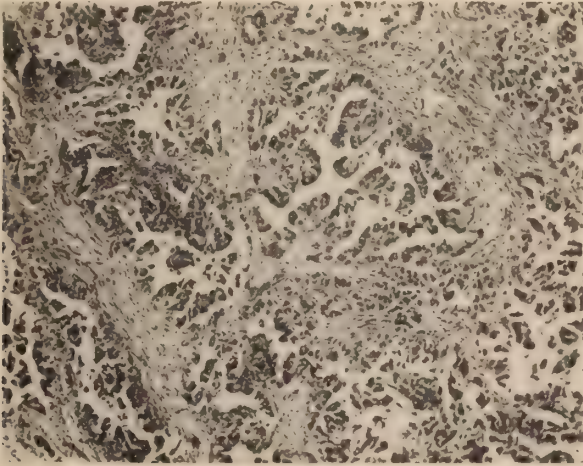


FIG. 1. Papillary adenocarcinoma

Considerable dispute still exists as to the nature of the class of tumor into which this case fits. Most pathologists believe that all testicular tumors arise from teratomas, whereas some believe that the papillary type of adenocarcinoma seen here probably originates in the rete testis. The Friedman test, or the strength of its titre cannot be used to differentiate the origin.

In determining the advisability of radical surgery in testicular neoplasms, including the removal of the regional lymph nodes, one must remember that such surgery is difficult and hazardous. On the other hand, seminomas of the testicle are very highly radiosensitive. The relative advantages and difficulties must be weighed in each instance.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D. *presiding*

Monday, February 10, 1941

*Case 3.*¹ Multiple Brain Abscesses and Incidental Finding of Hemangiomatous Malformation of the Midbrain

[From the Neurological Service of Dr. I. S. Wechsler]

History (Adm. 459148; P.M. 11573). A man, aged 51, first entered the hospital in 1927 because of dyspnea, abdominal swelling and precordial pain which radiated down the left arm and which was provoked by exertion. At that time a serological test for syphilis was found to be positive and anti-syphilitic therapy was begun. In the course of a neurological examination, a positive Romberg sign was detected and the finger-to-nose test with the right hand was executed poorly. His second admission (1929) was for treatment of bronchopneumonia. He returned to the hospital in 1930 after a diagnosis of bronchiectasis had been made in the Out-Patient Department. At that time, he complained also of severe pain in the right flank, but its origin remained undetermined. Slurring of speech, a zone of hyperesthesia at the level of the sixth and seventh thoracic segments on the right side, and sluggish superficial reflexes on the right side were the positive neurological findings. He continued to experience attacks of precordial pain radiating down the left arm. In the course of the next nine years he became subject to recurrent attacks of unconsciousness which were said to resemble "major" epileptic seizures, usually preceded by an attack of precordial pain. The attacks became more frequent and led to numerous admissions to several city hospitals. On the fourth and last admission to this hospital, he complained of an increase in the severity of his cough, bloody sputum, pain in the left chest, and severe chills for one week.

Examination. The patient appeared to be acutely ill and his temperature was elevated to 103°F. He coughed with production of mucopurulent sputum. There was clubbing of the fingers and toes. A large thyroid adenoma was noted on the left side of his neck. Examination of the heart was negative. The blood pressure was 140 systolic and 80 diastolic. There was a diminished percussion note with diminished breath sounds at both bases posteriorly, more marked on the left where pectoriloquy was present. The only positive neurological signs noted were small irregular pupils, which did not react to light.

Laboratory Data. Blood: The white blood cells numbered 18,300 of which there

¹ The first two cases were presented in a previous issue of the JOURNAL (Vol. VIII, No. 3).

were 89 per cent polymorphonuclear leucocytes; 9 per cent lymphocytes; and 2 per cent monocytes. The blood Wassermann and Kahn reactions were negative. The sputum contained pneumococci, Type III. The x-ray examination of the chest showed bronchopneumonia at both bases and some fluid at the left base.

Course. The patient was treated with sulfapyridine and his fever dropped to almost normal within two days. He developed hematuria, however, and the drug was discontinued. The temperature rose again and on the fifteenth hospital day a left thoracotomy was performed and a large quantity of purulent material was drained. On the twenty-second hospital day the patient had a severe attack of precordial pain and repeated electrocardiograms revealed the presence of posterior wall myocardial infarction. On the forty-first hospital day he suddenly became drowsy, and had an elevation of temperature, with increase in pulse rate and respirations. He rapidly became comatose, developed rigidity of the neck, bilateral Kernig sign,

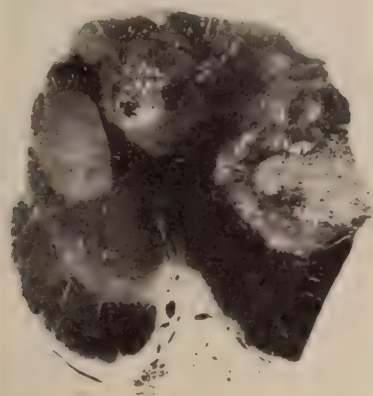


FIG. 9. The midbrain (myelin stain) in case 3

fixed pin-point pupils, slight paresis of the right upper and lower extremities, absence of abdominal reflexes, and a positive Oppenheim sign on the right. There was a questionable facial paresis on the right side. Lumbar puncture yielded turbid cerebrospinal fluid under increased pressure with 3,000 white blood cells per cubic millimeter, mostly polymorphonuclear leucocytes. The cerebrospinal fluid Wassermann, colloidal gold and globulin tests were all negative. The cerebrospinal fluid sugar was 45 mg. per cent and the total protein was 114 mg. per cent. A culture of the cerebrospinal fluid revealed *H. influenzae*; subsequent lumbar punctures revealed a decrease in the number of white blood cells, which became predominantly mononuclear. He was again placed on sulfapyridine, but he remained unimproved and died after four days of coma.

Necropsy Findings. Brain. Gross. The leptomeninges were dull and did not contain as much cerebrospinal fluid as normally. On the dorsal surface of the cerebellum, in the midline overlying the vermis and extending inferiorly towards the fourth ventricle and laterally over the cerebellar hemisphere was a thick, greenish exudate. The vessels of the brain were somewhat sclerotic.

On sectioning the brain, an enormous symmetrical hydrocephalus was found. The corpus callosum was thinned and the septum pellucidum destroyed. The third ventricle was slightly dilated. Multiple abscesses were found in the cerebrum measuring about 1 cm. in diameter and filled with a yellowish-green purulent diffuent exu-

date. One of these was situated in the right frontal lobe adjacent to the cortex of the premotor area. A second was found situated within the centrum ovale of the left

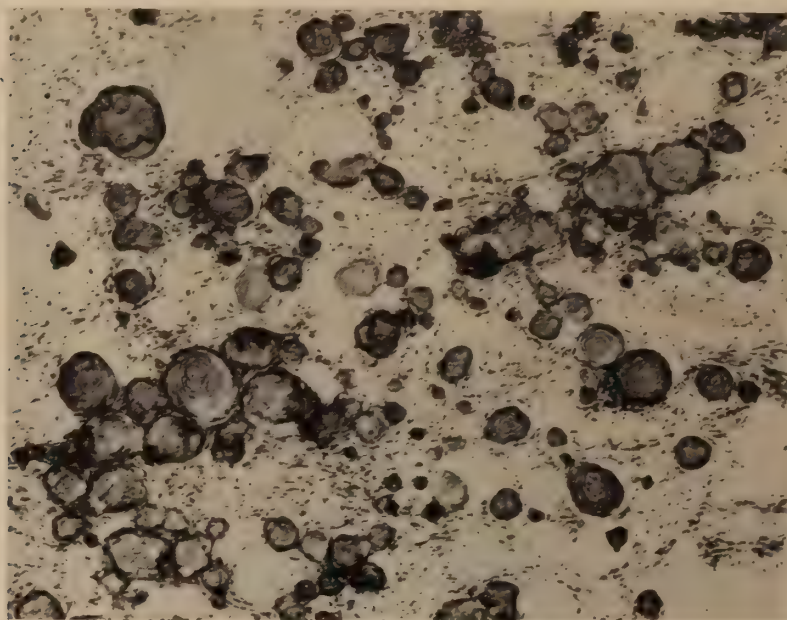


FIG. 10. Psammoma body in the hemangiomatous area on the left side of the mid-brain (case 3).

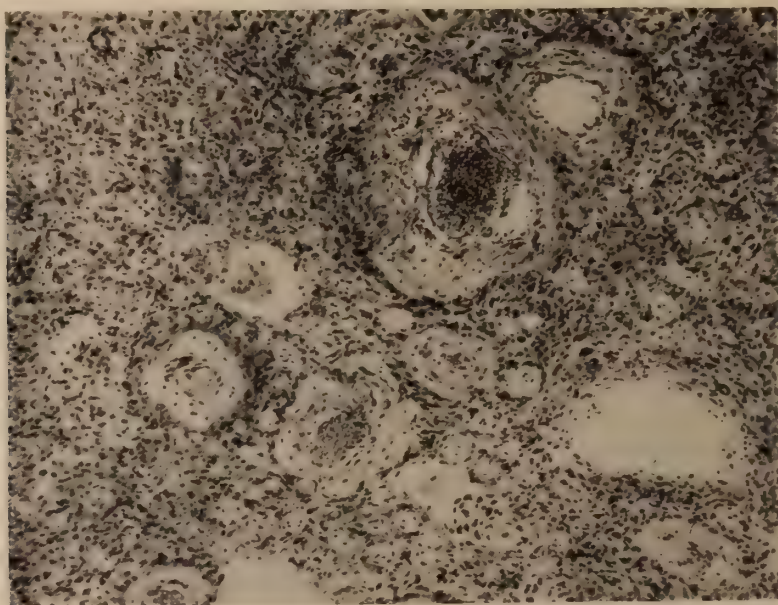


FIG. 11. Hemangiomatous formation in the peri-aqueductal area (case 3) occipital lobe. Two abscesses were present in the cortex and adjacent subcortex of the medial aspect of the left occipital lobe.

The aqueduct of Sylvius was somewhat narrowed and, near the fourth ventricle, was found to be obliterated by what appeared to be granulomatous tissue. In the

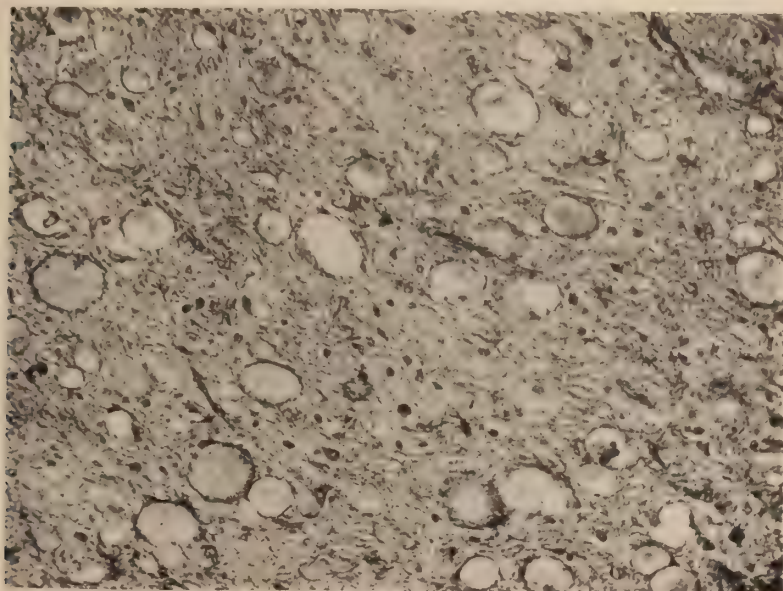


FIG. 12. Foam cells (case 3)

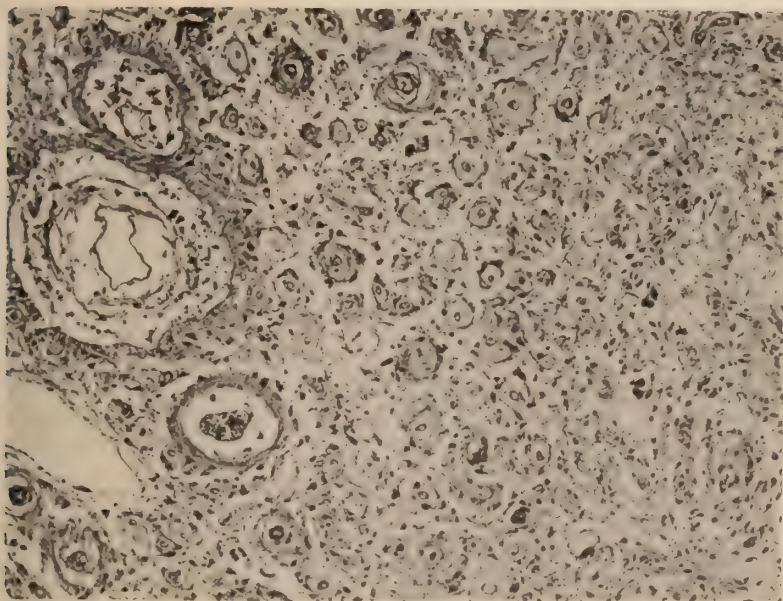


FIG. 13. Capillary hemangiomatous zone within the obliterated aqueduct (case 3)

anterior portion of the midbrain in the left lateral portion of its tegmentum, there was a round mass, yellowish-gray in color, presenting a granular surface, well demarcated from the rest of the tissue, measuring about $1\frac{1}{2}$ cm. in diameter.

Microscopic. Cerebral cortex: Section of cerebral cortex containing two small abscesses showed the latter to be surrounded by a zone of prominent and injected blood vessels, which in turn was enveloped by a zone of fibrous tissue. The adjacent brain tissue showed an increase in the glial elements including many gitter cells. The ganglion cells had darkly staining, eccentrically placed nuclei with homogeneous deeply staining cytoplasm, indicating early degenerative changes.

The meninges: The pia-arachnoid lining the cortex and the midbrain was infiltrated with polymorphonuclear leucocytes and mononuclear cells. There was a marked congestion of the glial and subependymal vessels. The ependymal lining in the lateral ventricles and the aqueduct was desquamated in places or covered by a purulent exudate.

The midbrain: A myelin stain revealed marked demyelination of the tectum and of the lateral aspect of the left part of the tegmentum encroaching upon the substantia nigra on that side (fig. 9). The aqueduct was displaced to the right and was smaller than normal. In the right dorso-lateral area of the tegmentum, there was an area of gray matter which was the posterior quadrigeminal body in an abnormal position. A similar section stained with hematoxylin and eosin showed the demyelinated areas in the dorsal and left lateral portions of the midbrain to consist of hemangiomatous tissue which was fairly sharply delineated from the adjacent tissue. In the lateral area of the midbrain there were large numbers of psammoma bodies (fig. 10) surrounded by a large number of elongated cells arranged in streams which had the appearance of fibroblasts. Adjacent to the aqueduct was an area containing many small and medium sized blood vessels (fig. 11) with thick muscular walls, some of which were filled with blood. Many foam cells were encountered (fig. 12). An occasional blood vessel showed calcified hyaline deposits in the wall.

In some sections the aqueduct was almost completely closed by numerous small capillaries and larger vessels (fig. 13). The latter constituted a hemangiomatous formation, which contained several very small irregularly placed canaliculi lined with ependyma, representing the only patent part of the aqueduct in this region.

The brain tissue adjacent to the tumor showed a relative increase in the glial elements. Some of the ganglion cells showed a moderate degree of nuclear disintegration and chromatolysis. The cells in the oculo-motor nuclei appeared to be essentially normal except for an apparent increase in the glial cells.

Comment. *Dr. Globus:* On his first admission, the patient already presented some neurological manifestations, which now in the light of the recently disclosed post-mortem findings, can be explained by the hemangiomatous malformation of the midbrain. The same is true of the sensory disturbances found in the same patient thirteen years later and of the accompanying complaints of pain in the same region. Even the then noted slurring speech and the sluggish superficial reflexes on the right side are not without significance. What is still more significant are the so-called epileptic seizures which marked his last nine years of life. They, in view of the mesencephalic lesion, were probably in the nature of decerebrate seizures, often associated with midbrain dysfunction.

The fatal issue in this case, of course, is to be traced to the pulmonary disease and, particularly, to the thoracotomy, causing multiple infected emboli, which resulted in the multiple brain abscesses.

Reported by *P. Myerson, M. D.*

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

The Severer Forms of Acute Appendicitis with Special Reference to the Treatment of Appendiceal Abscess E. E. ARNHEIM AND H. NEUHOF. Surg., Gynec. & Obst. 70: 42, January 1940.

Death should rarely follow operations for acute phlegmonous or gangrenous appendicitis, appendicitis with local peritonitis or appendicitis with abscess. This view is based on 212 surgical cases in ward service and in private practice from 1931 to 1939. There were four fatal cases, a mortality of 1.8 per cent. Three of the deaths were in cases in which diffuse peritonitis existed at the time of operation. There were no deaths in forty cases of acute appendicitis with abscess or in seventeen cases of acute appendicitis with local peritonitis. The low mortality (with the exception of that of diffuse peritonitis) is attributed essentially to certain principles in operative technic and in general management before and after operation.

Ureteropelvic Anastomosis following Arulsion. A. HYMAN AND S. F. WILHELM. J. Urol. 43: 52, January 1940.

Although traumatic separation of the ureter from the pelvis is rare, it was possible to collect and report five such instances. Each case occurred during the course of pyelotomy for calculus in the presence of renal infection. In three of these five cases a satisfactorily functioning kidney resulted from re-implantation of the ureter into the pelvis. The following principles are of the utmost importance: 1) The provision of free urinary drainage by means of a nephrostomy; 2) Accurate suture anastomosis of the ureter to the pelvis without tension; 3) Splinting of the anastomosis with a catheter to immobilize the ureter and maintain the stoma.

Grasping and Sucking. I. BIEBER. J. Nerv. & Ment. Dis. 91: 1, January 1940.

Investigation of grasping and sucking in infants, and in pathological states of adults, reveal that these phenomena are physiologically related. In new-borns and infants grasping can be elicited and maintained after sucking is induced. In certain pathological states of adults, such as semi-comatose and delirious conditions, grasping and sucking reappear, and bear a similar reciprocal relationship to one another. The well-known clinical symptoms of carphologia and sub-sultus tendinum are elaborations of grasping responses in deliria. The sucking movements that accompany this grasping have not been stressed, and its relation to grasping not noted. Grasping can be elicited by placing an object in the hand; sucking by touching the lips. The author also concluded that the biological function of grasping is initially supportive and after hand to mouth activity has been established it also serves to bring objects closer to the subject.

The Relationship of Bacillary Dysentery Infections to Chronic Intermittent Diarrheas.

R. TURELL. *Rev. Gastroentero.* 7: 14, January 1940.

It was pointed out that there exists no unanimity of opinion as to the criteria of an unequivocal diagnosis of diarrhea. The relationship of an antecedent bacillary dysentery infection to chronic ulcerative colitis was stressed. The difficulties of the isolation of the dysentery bacterium and the value of the serum agglutination tests were discussed.

There is a large group of cases of intermittent diarrhea where the agglutination tests are persistently positive in high titres, but other examinations give negative results. These patients are a source of discrimination of bacillary dysentery and should be the concern of the public health authority. This disease outranks typhoid fever in New York City.

An epidemiologic survey of bacillary dysentery should include a preliminary stool culture and a study of the agglutinins of the blood serum. In 10 to 14 days, another specimen of blood serum should be submitted for agglutination tests. A rising titre should be considered as suggestive diagnostic evidence of bacillary dysentery, as should a preliminary negative test and subsequent positive tests. Additional specimens of blood collected at weekly intervals for a month may be desirable. Cultural studies of the material obtained from the base of the ulcer, mucosal scrapings, and Lieberkuhn gland aspirations should be made, as they yield a higher percentage of positive results than do similar studies of dejecta.

Puberty, Menstruation, Pregnancy. R. T. FRANK. *Bull. New York Acad. Med.* 16: 83, February 1940.

A general survey of the endocrine forces which govern puberty, menstruation and pregnancy.

Puberty is a gradual process which comes to a climax with the onset of the menses, preceded by the development of the sex characters. The condition may be delayed by hypopituitarism, hypothyroidism, obesity or malnutrition.

The menstrual cycle indicates full maturation of the female. Hormonally it is marked by blood and excretory cycles due to periodic increase and decrease of the gonadotropic factors, estrogens, and progesterone.

Pregnancy at once produces a huge increase in the secretion of gonadotropic, estrogenic and progestational factors as well as an increase in the androgens. The chorionic epithelium is a temporary gland of internal secretion.

Functional disturbances of the cycle in most cases manifest themselves by a change in the hormonal secretion and excretion, but except in menorrhagia and metrorrhagia, where the excretion of estrogen is greatly increased, these assays do not completely clarify the situation. It seems established that variation in the secretion of gonadotropic, estrogenic and progestational factors bring about these functional disturbances of which amenorrhea, dysmenorrhea, sterility, menorrhagia, premenstrual tension are the clinical indicators.

The effect of estrogens in infantile gonorrhea and in the menopause are well established. Progesterone is distinctly promising in the treatment of dysmenorrhea and habitual abortion. The treatment of menorrhagia has been less successful. Estrogens are useless, gonadotropic extracts show no convincing effect. Androgens in the female must be given with caution because of the observed hirsutism, coarsening of voice, and increase of the clitoris noted in some cases. The extracts prepared from the prepituitary gland itself are not as yet available. Pregnant mare's serum may prove of value but must be given with caution because of the possibility of severe allergic reactions.

Congenital Diaphragmatic Hernia. Report of a Case with Sudden Death. J. J. KRISTAL. *Arch. Pediat.* 57: 76-91, February 1940.

Diaphragmatic hernia has presented itself as a diagnostic problem since little attention has been given to the condition by the clinician. This paper is presented in text-book style including a review of the literature from Paré in 1579, who first described the condition, to the present.

The case herein presented is of unusual interest since only one other case has been found in the literature where sudden death occurred. The patient was a 15 month old white female, practically asymptomatic, who died within 5½ hours after admission to the hospital.

The autopsy revealed a congenital diaphragmatic hernia which had been unrecognized on admission. It was the most common type of hernia, namely, through the left pleuro-peritoneal hiatus. The cause of death was a strangulated hernia.

The case, as well as the theoretical cause of death, is fully discussed from the physiological angle.

Evaluation of Roentgenography of Surgically Exposed Kidney in the Treatment of Renal Calculi. G. D. OPPENHEIMER. J. Urol. 43: 2, February 1940.

An analysis was made of patients who had operative x-ray control during the years 1928 to 1938. Eighty-five patients were so treated. In 29 patients (34 per cent) stones or stone fragments which could not be palpated or found without the roentgenogram were located by means of this procedure and removed. The method is not a 100 per cent correct one, however, and had a percentage error of 12.7 per cent. Illustrative cases and x-rays were presented and it was concluded that the procedure is a most valuable one in the operative treatment of renal calculi.

Varicelliform Eruption Resulting from Sulfanilamide Therapy. O. L. LEVIN AND H. T. BEHRMAN. Urol. & Cut. Rev. 44: 114, February 1940.

The occurrence of a varicelliform eruption following the administration of sulfanilamide is reported. The previous reports of purpuric and scarlatiniform eruption, toxic dermatoses, exfoliative dermatitis, and generalized erythematous dermatitides are mentioned. The appearance of this type of eruption should be kept in mind as another of the cutaneous manifestations of toxicity from sulfanilamide therapy.

Interlobar Perforated Abscess of the Lung (Interlobar Empyema). H. NEUHOF AND B. COPLEMAN. Surg. 7: 236, February 1940.

In all the authors' cases, interlobar empyema proved to be an interlobar collection of pus due to rupture of a pulmonary abscess facing an interlobar surface. There are no clinical criteria for its recognition. The roentgenologic criteria are: an interlobar collection of fluid or of fluid and air; a fluid level on or near a fissure; progression of disease along a fissure. These distinctive features occurred in more than one-half the cases, but were obscured by overlying pleuritis in the remainder. The interlobar situation of the abscess often is not realized until the time of operation. The mortality of interlobar ruptured abscess is referable to prolonged delay in diagnosis, erroneous roentgenologic interpretation, and operative treatment which does not take into account the causative pulmonary abscess or which results in infection of the free pleural space. Thus the recognition of the fact that so-called interlobar empyema is due to the perforation of a ruptured pulmonary abscess is of clinical importance.

Cutaneous Manifestations of Vitamin A Deficiency in Children. E. LEHMAN AND H. G. RAPAPORT. J. A. M. A. 114: 386, February 1940.

Nine children, almost all of families on relief, had cutaneous manifestations of vitamin A deficiency similar to those described by Frazier, Hu and others. The dermal lesions consisted particularly of horny papules formed by keratotic plugs projecting from hair follicles. The diagnosis was confirmed by photometric studies. Improvement of the visual tests in some children was immediate with single adequately large doses of vitamin A but in others required prolonged intensive therapy. Maximal improvement of the skin was attained with a daily dose of from 100,000 to 300,000 International Units of vitamin A in from two to four months. So far these investigations indicate that keratosis pilaris, ichthyosis follicularis and other synonyms are merely descriptive terms for the cutaneous manifestations of vitamin A deficiency.

Diabetes Mellitus In One of Identical Twins. A. E. FISCHER. Am. J. Dis. Child. 59: 386, February 1940.

Diabetes mellitus in one of a pair of identical twin girls was discovered at the age of 3 years, 11 months. The twins have been followed for six years. Growth has been slightly retarded in the diabetic child. However, their weights are approximately the same. The non-diabetic twin has had frequent glucose tolerance curves which were normal except when the test was made after an acute infection. This child does not show any evidence of diabetes mellitus, although her heredity suggests that she will probably become diabetic later in life.

A COURSE IN STATISTICAL METHODS

An introductory course in Statistical Methods is being initiated at The Mount Sinai Hospital which will be given by Dr. Franklin Hollander. The course is intended for medical men who wish to familiarize themselves with the procedures used in the statistical treatment of clinical and laboratory data. It will include the solution of practical problems as well as formal lectures.

The course will run for a period of ten weeks (total of thirty hours) and will be given 2 afternoons a week, 4 to 5:30 p.m., starting about December 1, 1941. Applications for the course should be sent to Miss Edith L. Levy, Secretary for Medical Instruction at the Hospital.

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CONTENTS*

	PAGE
FOREWORD. <i>George Bachr, M.D.</i>	xiii
IN THE BEGINNING. <i>Howard Lilienthal, M.D.</i>	321
BE AN OPTIMIST. <i>Bernard Sachs, M.D.</i>	323
DR. B. S. OPPENHEIMER'S CONTRIBUTIONS TO POST-GRADUATE MEDICAL EDUCATION. <i>Joseph Turner, M.D.</i>	326
RESTING BLOOD FLOW AND PERIPHERAL VASCULAR RESPONSES IN DIFFERENT PORTIONS OF THE EXTREMITIES. <i>David I. Abramson, M.D.</i>	328
ACUTE GENERALIZED POSTOPERATIVE PERITONITIS SIMULATING CORONARY ARTERY THROMBOSIS. <i>Samuel H. Averbuck, M.D.</i>	335
BROWN-SEQUARD SYNDROME IN ASSOCIATION WITH TUBERCULOUS SPONDYLITIS AND PULMONARY SILICO-TUBERCULOSIS. <i>Lewellys F. Barker, M.D.</i>	341
THE SIGNIFICANCE OF NEGATIVE T WAVES IN ALL THREE STANDARD LEADS OF THE ELECTROCARDIOGRAM. <i>Arlie R. Barnes, M.D., and H. B. Burchell, M.D.</i>	346
PAROXYSMAL TACHYCARDIA IN VERY EARLY INFANCY. <i>Murray H. Bass, M.D.</i>	357
PERICARDITIS AND SUBACUTE BACTERIAL ENDOCARDITIS. <i>David Beck, M.D.</i>	364
CORONARY ARTERY DISEASE, OBSERVATIONS ON DISPENSARY PATIENTS. <i>Julian E. Benjamin, M.D., H. Landt, M.D., and M. Landen, A.B.</i>	376
LIGATION OF THE SPLENIC ARTERY FOR THROMBOCYTOPENIC PURPURA AND CONGESTIVE SPLENOMEGALY. <i>Albert A. Berg, M.D., and Na- than Rosenthal, M.D.</i>	382

*The following articles: Desoxycorticosterone, George W. Thorn, M.D.; A Short History of the Treatment of Addison's Disease, Louis J. Soffer, M.D. and Frank L. Engel, M.D.; New Aspects of Pulmonary Tuberculosis and Their Relation to Treatment, Edgar Mayer, M.D. and Israel Rappaport, M.D. were submitted for publication in this volume, but will appear in a subsequent issue.

	PAGE
ECHINOCOCCUS CYST OF THE LIVER: PROLONGED COURSE WITH OPERATIVE REMOVAL AND COMPLICATING THROMBOSIS OF THE PORTAL VEIN. <i>Solon S. Bernstein, M.D.</i>	399
SELECTIONS FROM THE NOTEBOOK OF A HOSPITAL ADMINISTRATOR. <i>E. M. Bluestone, M.D.</i>	409
A NOTE ON THE RELATIONSHIP BETWEEN JAUNDICE IN PIGS AND JAUNDICE IN HUMAN BEINGS. <i>George Blumer, M.D.</i>	418
ANGINA PECTORIS AND THE PEPTIC ULCER SYNDROME. <i>Ernst P. Boas, M.D. and Hyman Levy, M.D.</i>	422
THE KIDNEYS IN SUBACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS. <i>Henry A. Christian, M.D.</i>	427
AGENESIS OF THE CEREBELLUM (VERIFIED BY OPERATION). <i>Ira Cohen, M.D.</i>	441
SURGICAL PROBLEMS IN THE TREATMENT OF GASTRIC ULCER. <i>Ralph Colp, M.D.</i>	447
THE HEART IN FAT EMBOLISM. <i>Lewis A. Conner, M.D.</i>	454
QUANTITATIVE FORMULATION OF MAXIMUM URINARY SPECIFIC GRAVITY. <i>A. C. Corcoran, M.D. and Irvine H. Page, M.D.</i>	459
THE DIAGNOSIS OF ANEURYSM OF THE HEART. <i>J. Hamilton Crawford, M.D.</i>	469
PERSISTENT AURICULAR PREMATURE SYSTOLES OBSERVED FOR TWENTY-FOUR YEARS: CASE REPORT. <i>Arthur C. DeGraff, M.D. and R. C. Batterman, M.D.</i>	476
A NOTE ON THE INHERITANCE OF CARDIOVASCULAR DISEASE—RESULT OF INSURANCE INVESTIGATIONS. <i>Louis I. Dublin, Ph.D. and H. H. Marks</i>	482
THE NEPHROTIC CRISIS. <i>Kendall Emerson, Jr., M.D. and Donald D. Van Slyke, Ph.D.</i>	495
THE AURICULAR WAVE (P) OF THE HUMAN ELECTROCARDIOGRAM IN NORMAL AND PATHOLOGICAL STATES. <i>Harold Feil, M.D.</i>	502
THE USE OF SULFONAMIDES IN RENAL INSUFFICIENCY. <i>Arthur M. Fishberg, M.D.</i>	509
THE ESTROGENIC REACTIONS IN ADRENAL CORTICAL CARCINOMA. <i>Robert T. Frank, M.D.</i>	514
THE PATHOGENESIS OF COARCTATION OF THE AORTA—A NEW THEORY. <i>Charles K. Friedberg, M.D.</i>	520
THERAPEUTIC AGENTS AND RENAL IMPLANTATIONS IN EXPERIMENTAL HYPERTENSION. <i>Ben Friedman, M.D., J. Jarman, M.D. and J. Marrus, M.Sc.</i>	534
SUPPURATIVE TENOSYNOVITIS OF THE HAND. <i>John H. Garlock, M.D.</i>	540
PROPHYLACTIC IMPLANTATION OF ESTROGENS FOLLOWING SURGICAL AND RADIUM CASTRATION. <i>Samuel H. Geist, M.D., Robert I. Walter, M.D., and Udall J. Salmon, M.D.</i>	543

	PAGE
INTRACRANIAL ANEURYSMS: THEIR ORIGIN AND CLINICAL BEHAVIOR IN A SERIES OF VERIFIED CASES. <i>Joseph H. Globus, M.D. and Joseph M. Schwab, M.D.</i>	547
STUDIES ON EXPERIMENTAL HYPERTENSION. XVI. THE EFFECT OF HYPOPHYSECTOMY ON EXPERIMENTAL RENAL HYPERTENSION. <i>Harry Goldblatt, M.D., S. Braden, M.D., J. R. Kahn, M.D. and W. A. Hoyt, M.D.</i>	579
DEVELOPMENT OF KNOWLEDGE CONCERNING THE MEASUREMENT AND RHYTHM OF THE PULSE (HEROPHILUS, GALEN, CARBOLIENSIS, STRUTHIUS, GALILEO, FLOYER). <i>Walter W. Hamburger, M.D.</i> ...	585
VASCULAR ALLERGY. II. MANIFESTATIONS OF POLYVALENT SEN- SITIZATION. <i>Joseph Harkavy, M.D.</i>	592
THE EFFECT OF ROENTGEN THERAPY IN PRIMARY CANCER OF THE BREAST. <i>William Harris, M.D.</i>	606
CLINICAL SYNDROMES PRODUCED BY TEMPORARY DISTURBANCES OF THE CEREBRAL CIRCULATION. <i>Tinsley R. Harrison, M.D.</i>	612
COMPLEMENT TITRATIONS IN HUMAN SERA. <i>Michael Heidelberger, Ph.D.</i>	622
ON MECHANISMS OF INSPIRATORY FILLING OF THE CERVICAL VEINS AND PULSUS PARADOXUS IN VENOUS HYPERTENSION. <i>William M. Hitzig, M.D.</i>	625
TREATMENT OF ATONIC NEUROGENIC BLADDER BY TRANSURETHRAL RESECTION. <i>Abraham Hyman, M.D. and H. E. Leiter, M.D.</i>	645
DYNAMICS OF SYMPTOM PRODUCTION IN SPLENOMEGALY. <i>Raphael Isaacs, M.D.</i>	651
AN EARLY CASE OF HORSESHOE KIDNEY. <i>Saul Jarcho, M.D.</i>	656
THE NEURO-PSYCHIATRIC MANIFESTATIONS OF VITAMIN DEFICIENCIES. <i>Norman Jolliffe, M.D.</i>	658
MECHANISM OF HEART FAILURE. <i>Louis N. Katz, M.D.</i>	668
SPONTANEOUS PERIRENAL HEMATOMA. <i>Chester Keefer, M.D.</i>	682
THE SIGNIFICANCE OF PLASMA AND BLOOD VOLUME STUDIES IN CLINI- CAL MEDICINE. <i>Norman M. Keith, M.D.</i>	692
RELATION OF ANOXEMIA TO JAUNDICE IN LOBAR PNEUMONIA. <i>Fred- erick H. King, M.D., and Alan Leslie, M.D.</i>	703
PLEURAL MESOTHELIOMA. <i>Paul Klemperer, M.D., and Cesare Tedes- chi, M.D.</i>	710
ACUTE PERFORATIONS OF THE GASTRO-INTESTINAL TRACT DURING HOSPITAL OBSERVATION. <i>Percy Klingenstein, M.D., and Lester R. Tushman, M.D.</i>	721
OCULAR TENSION AND INTRAOCULAR CIRCULATION. <i>Carl Koller, M.D.</i>	731
A CONGENITAL CARDIAC ANOMALY: ATRESIA OF MITRAL ORIFICE AND SEPARATION OF LEFT AURICLE AND VENTRICLE. <i>Edward B. Krumbhaar, M.D.</i>	737

	PAGE
PRESSOR KIDNEY EXTRACTS ("RENIN") AND THE PRODUCTION OF CARDIAC AND GASTRO-INTESTINAL HEMORRHAGES AND NECROSIS IN DOGS WITH ABNORMAL RENAL CIRCULATION. <i>Louis Leiter, M.D., Ph.D., and Lillian Eichelberger, Ph.D.</i>	744
THE ASSOCIATION OF ANGINA PECTORIS OR CORONARY THROMBOSIS WITH MITRAL STENOSIS. <i>Samuel A. Levine, M.D., and A. J. Kawar, M.D.</i>	754
PAROXYSMAL AURICULAR FIBRILLATION AND FLUTTER WITHOUT SIGNS OF ORGANIC CARDIAC DISEASE IN TWO BROTHERS. <i>Robert Levy, M.D.</i>	765
FIVE YEARS OF CANCER RESEARCH. <i>Richard Lewisohn, M.D.</i>	771
NOTES ON CLINICAL OBSERVATIONS AND METHODS. II. <i>Emanuel Libman, M.D.</i>	777
NEPHROSIS AND THE "NEPHROTIC SYNDROME." <i>Leopold Lichtwitz, M.D.</i>	782
INVOLVEMENT OF THE HEART IN SARCOIDOSIS OR BESNIER-BOECK-SCHAUMANN'S DISEASE. <i>Warfield T. Longcope, M.D., and Arthur M. Fisher, M.D.</i>	784
ADAMANTINOMA OF THE HYPOPHYSAL DUCT. <i>Wallace G. MacCallum, M.D.</i>	798
THE UTERINE ELECTROCARDIOGRAM. <i>Hubert Mann, M.D., and Max D. Mayer, M.D.</i>	805
URINARY EXCRETION OF CAPON COMB GROWTH PROMOTING SUBSTANCES IN GRAVES' DISEASE AND MYXEDEMA AND MODIFICATIONS FOLLOWING IODINE AND DESICCATED THYROID THERAPY. <i>David Marine, M.D., and Samuel H. Rosen, M.D.</i>	811
NOMENCLATURE OF CORONARY ARTERY DISEASE: THE DIFFERENTIATION OF ANGINA PECTORIS, CORONARY INSUFFICIENCY AND CORONARY OCCLUSION. <i>Arthur M. Master, M.D., Harry L. Jaffe, M.D., Simon Dack, M.D., and Arthur Grishman, M.D.</i>	820
OTITIC INFECTIONS DUE TO THE PNEUMOCOCCUS TYPE III. <i>Jack L. Maybaum, M. D., and Joseph G. Druss, M.D.</i>	829
PIONEERS IN CARDIOVASCULAR SYPHILIS. <i>Edwin P. Maynard, M.D.</i> ..	841
THE USE OF HIGH FAT AND HIGH PURINE DIETS IN THE DIAGNOSIS OF GOUT. <i>Currier McEwen, M.D.</i>	854
EXPERIMENTAL HOLES IN THE RETINA. <i>Henry Minsky, M.D.</i>	863
DUODENAL ULCER FOLLOWING ACUTE INJURY OF THE SPINAL CORD. <i>Sylvan E. Moolten, M.D.</i>	868
THE VALIDITY OF NEPHROSIS AS A NOSOLOGICAL CONCEPT. <i>Eli Moschcowitz, M.D.</i>	878
PUTRID EMPYEMA WITHOUT FETID SPUTUM ("SURPRISE" EMPYEMA). <i>Harold Neuhoof, M.D.</i>	892

	PAGE
A NEW METHOD FOR THE TREATMENT OF LEUCOPENIC STATES. <i>Reuben Ottenberg, M.D.</i>	895
ELECTROCARDIOGRAMS WITH NORMAL LIMB LEADS AND WITH AB- NORMALITY IN ONLY ONE OF FOUR PRECORDIAL LEADS. <i>Harold</i> <i>E. B. Pardee, M.D.</i>	898
SOME COMPENSATORY MECHANISMS IN HEART FAILURE. <i>Abraham</i> <i>Penner, M.D., and Alice I. Bernheim, M.D.</i>	901
THE INFLUENCE OF PROTEIN METABOLISM ON THE DISTRIBUTION OF NITROGEN COMPOUNDS IN THE LIVER. <i>Ernest P. Pick, M.D.,</i> <i>and S. Glaubach, Ph.D.</i>	909
THE RELATIONSHIP OF BENIGN AND MALIGNANT HYPERTENSION. <i>George W. Pickering, M.D.</i>	916
LUNG ABSCESS. <i>Daniel Poll, M.D.</i>	922
POSTOPERATIVE PRECIPITATION OF VITAMIN B COMPLEX DEFICI- ENCIES. <i>Herbert Pollack, M.D., Max Ellenberg, M.D., and</i> <i>Henry Dolger, M.D.</i>	925
A QUANTITATIVE METHOD FOR DETERMINING COLLATERAL CORONARY CIRCULATION. <i>Myron Prinzmetal, M.D., S. Kayland, M.D., C.</i> <i>Morgoles, M.D., and L. Tragerman, M.D.</i>	933
DISPLACEMENT OF THE RS-T SEGMENT BY POTASSIUM CHLORIDE. <i>Jane Sands Robb, M.D., M. S. Dooley, M.D., and R. C. Robb,</i> <i>M.D.</i>	946
INSULIN HYPOGLYCEMIA AND VASCULAR ACCIDENTS IN DIABETES MELLITUS. <i>Howard F. Root, M.D., and C. W. Styron, M.D.</i>	953
THE MECHANISM OF AURICULAR FLUTTER AND FIBRILLATION. An Historical Survey. <i>Irving R. Roth, M.D.</i>	965
AVIATION MEDICINE. <i>Leonard G. Rowntree, M.D.</i>	980
HYPERTENSION ASSOCIATING UTERINE FIBROIDS: CONSIDERED FROM VIEWPOINT OF ETIOLOGICAL CONNECTION AND SURGICAL RISK (BASED ON A REVIEW OF 500 CASES). <i>Isidor C. Rubin, M.D.,</i> <i>and A. M. Davids, M.D.</i>	987
THE PROBLEM OF ALLERGY IN RHEUMATIC DISEASE. <i>Bela Schick,</i> <i>M.D.</i>	991
BILATERAL THROMBOSIS OF THE POSTERIOR CEREBRAL ARTERIES. <i>Kaufman Schlivek, M.D.</i>	995
INOCULATION MALARIA AND DRUG ADDICTION. <i>Emanuel B. Schoen-</i> <i>bach, M.D., and Clifford L. Spingarn, M.D.</i>	998
TRANSIENT VENTRICULAR FIBRILLATION. <i>Sidney P. Schwartz, M.D.</i>	1005
THROMBO-ANGIITIS OBLITERANS AND POLYCYTHEMIA VERA. <i>Samuel</i> <i>Silbert, M.D.</i>	1021
THE BLOOD IODINE IN THE PERIOD AFTER THYROIDECTOMY—PRE- LIMINARY REPORT. <i>Solomon Silver, M.D., and B. Magasanik,</i> <i>B.S.</i>	1027

	PAGE
METHYLATION OF HYDROXYL GROUPS IN TRIAZINES. Studies on Triazines. <i>Harry Sobotka, Ph.D., and Edith Block, Ph.D.</i>	1032
SYPHILITIC AORTITIS WITH AORTIC REGURGITATION—AN ELECTROCARDIOGRAPHIC AND AUTOPSY SURVEY AT THE MASSACHUSETTS GENERAL HOSPITAL. <i>Howard B. Sprague, M.D.</i>	1034
COMPARISON OF SIMULTANEOUS INDIRECT (AUSCULTATORY) AND DIRECT (INTRAARTERIAL) MEASUREMENTS OF ARTERIAL PRESSURE IN MAN. <i>J. Murray Steele, M.D.</i>	1042
THE PERIPHERAL BLOOD FLOW IN TEN WOMEN EXHIBITING GRAVES' DISEASE. <i>Harold J. Stewart, M.D., and W. F. Evans, M.D.</i>	1051
MASSETER AND TEMPORAL MUSCLE TENDERNESS IN SYPHILITIC TRIGEMINAL NEURITIS. <i>Israel Strauss, M.D.</i>	1060
THE ROENTGENKYMোগRAM IN MYOCARDIAL INFARCTION. III. Cases with Normal Electrocardiograms. <i>Marcy L. Sussman, M.D., and Simon Dack, M.D.</i>	1064
THE NEUROLOGICAL MANIFESTATIONS OF PERIARTERITIS NODOSA. <i>Israel S. Wechsler, M.D., and Morris B. Bender, M.D.</i>	1071
SELF-OBSERVATIONS AND PSYCHOLOGIC REACTIONS OF MEDICAL STUDENT A.S.R. TO THE ONSET AND SYMPTOMS OF SUBACUTE BACTERIAL ENDOCARDITIS. <i>Soma Weiss, M.D.</i>	1079
CESSATION OF REPEATED PULMONARY INFARCTION AND OF CONGESTIVE FAILURE AFTER TERMINATION OF AURICULAR FIBRILLATION BY QUINIDINE THERAPY. <i>Paul D. White, M.D., and Herrman L. Blumgart, M.D.</i>	1095
FACTORS AFFECTING THE OUTCOME IN ACUTE INFARCTION OF THE MYOCARDIUM. <i>Frederick A. Willius.</i>	1104
CONCERNING THE FORM OF THE QRS DEFLECTIONS OF THE ELECTROCARDIOGRAM IN BUNDLE BRANCH BLOCK. <i>Frank N. Wilson, M.D.</i>	1110
ULCER IN MECKEL'S DIVERTICULUM. UNIQUE ROENTGENOLOGIC FINDINGS. <i>Asher Winkelstein, M.D.</i>	1118
RELATIONSHIPS BETWEEN BILIARY TRACT DISEASE AND HEART DISEASE. <i>Charles C. Wolferth, M.D.</i>	1121
PHYSICAL MEASURES IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE. <i>Irving S. Wright, M.D.</i>	1128
CALCIFICATION OF THE PERICARDIUM AND CHRONIC CARDIAC COMPRESSION: REPORT AND DISCUSSION OF FOUR CASES. <i>Wallace M. Yater, M.D.</i>	1144
OLD AGE IN ANCIENT EGYPT. A Contribution to the History of Geriatrics. <i>Frederic D. Zeman, M.D.</i>	1161
ABSTRACTS	1166
BOOK REVIEWS	1176

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DR. BERNARD S. OPPENHEIMER

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ON THE OCCASION OF HIS SIXTY-FIFTH BIRTHDAY
BY HIS FRIENDS, ASSOCIATES AND PUPILS



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TO DR. BERNARD SUTRO OPPENHEIMER,
AN ESTEEMED COLLEAGUE, WHO
HAS GIVEN THIRTY-SEVEN YEARS OF
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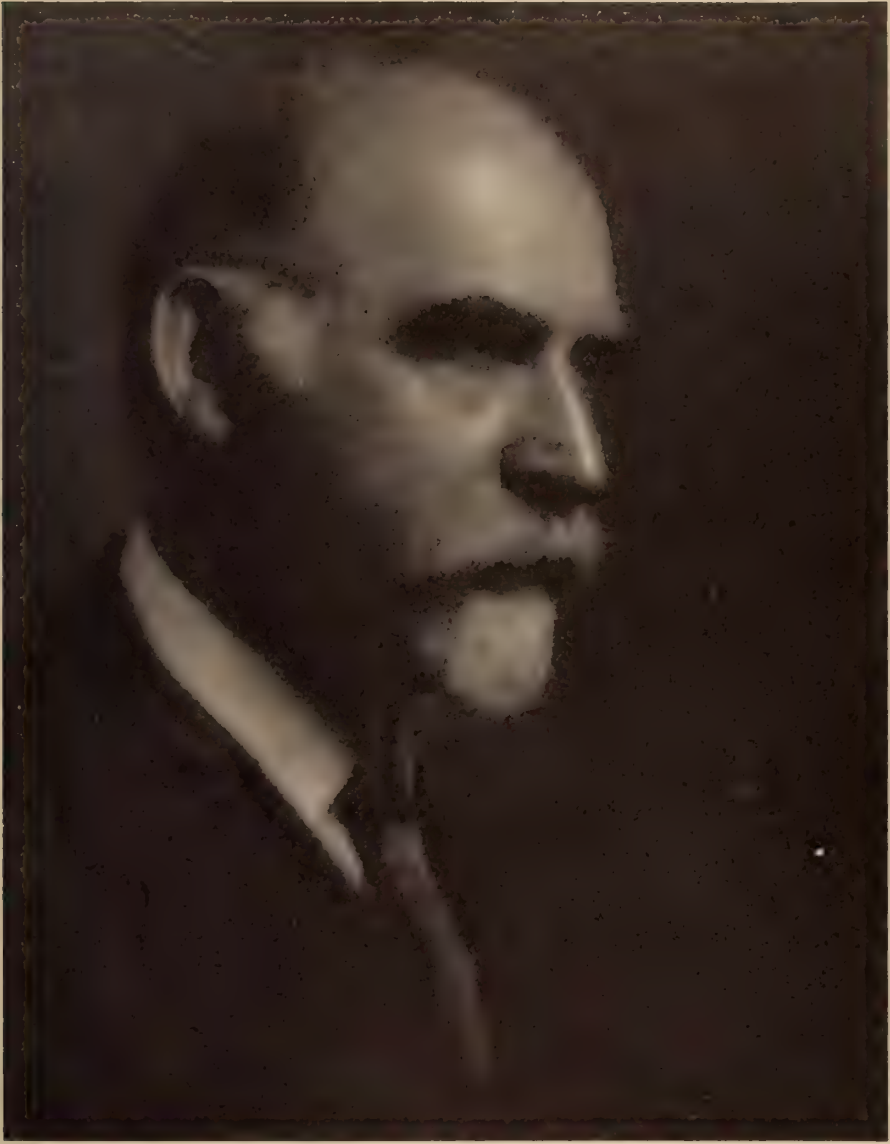
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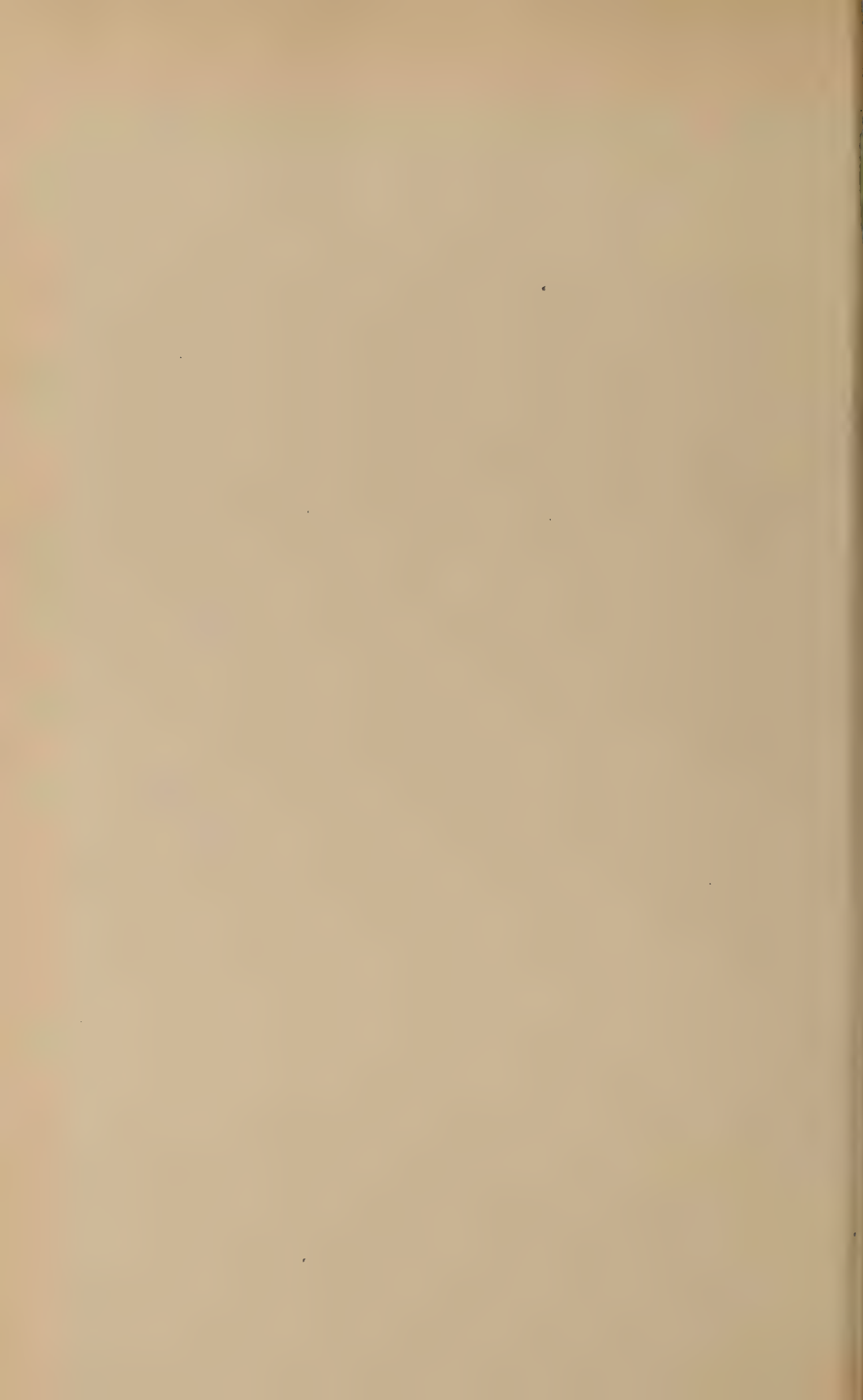
FOREWORD

The many friends and associates of Dr. Bernard Sutro Oppenheimer welcome the opportunity to record their esteem and affection by contributing to this commemorative volume. Numerous as they are, the contributors to this volume form only part of a much larger company of scientists and clinicians in all parts of the world who have learned to know and admire Dr. Oppenheimer through personal or scientific contacts during the last forty years.

Forty years of professional activities and scientific labors have not dimmed his ardor as a clinician or investigator. He began his career as a pioneer in the new field of cardiovascular physiology which had just been opened up by Mackenzie, Lewis and Einthoven. In his many publications since that time are revealed his constant interest in the application of new physiological observations to the interpretation of problems of clinical medicine. At the bedside his attention is primarily centered upon revealing and correcting the physiological disturbances of the disease process. It is, therefore, not surprising that his clinical and scientific interest extended from the realm of cardiovascular diseases to the new field of endocrinology in which he has made many contributions.

Throughout his career, his unflagging scientific and clinical zeal has been a stimulus and inspiration to a generation of young clinicians who have had the privilege of serving under his leadership. His wide acquaintanceship with important personalities in medicine and the basic sciences has helped to bring them and the influence of their work to our Hospital. He has served to enrich the medical lives of all of us who have worked at The Mount Sinai Hospital. This volume is a small expression of our gratitude and affection.

GEORGE BAEHR



IN THE BEGINNING

HOWARD LILIENTHAL, M.D.

Dr. Oppenheimer has become a great physician not merely because of his education in the science and art of Medicine but because of his logical methods in dealing with the cases of those who sought his advice and because of his sympathetic approach in their troubles.

In the early nineties the competitive examinations for places on the House Staff of The Mount Sinai Hospital in New York attracted many ambitious young men. The tests were in three separate sittings; a written, a practical and an oral. Every one who applied was permitted to take the examination and, according to his rating, he might be granted his preference in surgery or internal medicine.

In those days of nearly forty years ago a large number of recently graduated physicians, as well as many who had not yet completed the course in the Medical School, were anxious to secure House Staff positions. There were from thirty to fifty or more applicants each year. Following two years of service the Hospital issued a diploma which was greatly valued as an evidence of proficiency. There were one year terms also, leading to certification though not to the diploma.

The committee on examination was composed of Attending Physicians with an occasional Adjunct or Associate.

It must have been about 1901 when I was one of the examiners and, proud of the job, I composed a list of questions and selected problems for the surgical part of the program.

My subject for the practical examination was a boy, nine years old, about to be discharged after his surgical convalescence. There had been an amputation through the right hip-joint followed by primary union. There was also a linear scar through the right rectus abdominis muscle. His general condition was excellent; no nodes or other masses were palpable anywhere.

"Doctor Doe," I addressed the candidate, "What do you think was the reason for amputation in this case?" My second query was concerned with the right abdominal scar.

Privilege was given for physical examination and many of the men took full advantage of this. Only the one taking the test was permitted to be in the room with the examiner and the request was made that there be no discussion on the surgical aspects of the case with those who were awaiting their turn.

A majority of the applicants believed that the amputation had been

done because of trauma of the femur, probably sustained in a street accident. Nearly all thought that the abdominal scar had no connection with the amputation and that reference to it may have been in the nature of a catch-question. Some suggested that it might have been the mark of an independent operation, perhaps an appendectomy. Interrogating the patient was forbidden and he seemed to be amused by the apparent discomfiture of the doctors.

Then entered a tall dignified young man whose appearance was thoroughly professional; he might have been a member of the Attending Staff. From the list I learned that he was Bernard Sutro Oppenheimer, from the graduating class of the College of Physicians and Surgeons. When he had observed, palpated and auscultated our problem he announced that, in his opinion, the amputation had been performed by exarticulating the right hip and that the reason for the procedure was, probably, not because of infection or trauma but that it might have been done in order to remove a new-growth of the bone which could not have been otherwise extirpated. He explained the linear abdominal cicatrix as the result of an incision to permit examination of the pelvis from within and also, perhaps, as an approach for digital compression of the common iliac artery to control hemorrhage during the amputation.

This was, in truth, the correct analysis of the case.

Two other contestants, both of them convincing and impressive in manner and appearance, arrived at the same conclusion by almost identical reasoning.

Not one of the three leading competitors felt inclined to choose a position in surgery. One of them insisted that all he desired was a year in the Hospital so that he might learn first-hand how such an institution should be organized and managed. He was awarded this privilege. His name is Sigismund S. Goldwater and we all know how wise he was in his selection.

The third one to arrive at the correct solution was Alfred Fabian Hess, later a world-renowned pediatrician who made great contributions to the physiological chemistry of food materials. We shall always mourn his untimely passing.

Dr. Oppenheimer, now one of our consulting staff, is an eminent cardiologist. He is well and working. Long may he be with us to blaze the way.

BE AN OPTIMIST

B. SACHS, M.D.

[*New York*]

I am happy to be asked to contribute to the volume in honor of Doctor Oppenheimer, whose scientific work in the domain of cardiac disease deserves the recognition and praise it has received here and abroad. I know that I can add little to the treatment of heart disease; it may even be presumptuous on my part to say anything, but I have one message which I must transmit to the cardiologist and above all to the general practitioner (may I say the "family physician"?). I am especially prompted to say all this because I know how gladly Doctor Oppenheimer would subscribe to my sentiments, having seen him at work in the wards and in private practice.

As a neuro-psychiatrist who has been active over half a century I have emerged as an optimist. Many a time I have been tempted to write an article on "Things are not as bad as they seem". Do not tell the patient all you know or all you think you know. Above all, do not be overawed by your rapidly accumulating knowledge of curves and electrocardiograms—a knowledge so much greater than your predecessors of a few decades ago could boast. What I ask is, does the present-day sufferer from heart disease live longer than a similar sufferer of the late nineties? Some may, many do not. The patient appreciates the doctor's vast learning and his thoroughly modern methods as I do too; but very often, nine times out of ten, the patient while duly impressed has lost confidence in himself, has been made an introvert and has been filled with fear and despair, just waiting for the end to come.

Often enough I have been reminded of my old master, Kussmaul, who watched a candidate for a degree examining a man ill with typhoid fever and subjecting him to every possible test; "H., you may think you know all about this man, but you have never for one moment thought of the discomfort and misery your examination has caused. If I see you doing that again, I will let you flunk." (H. heeded the warning and a few years later was appointed one of Kussmaul's assistants.)

The moral of all this is treat the patient not the disease. In modern phrase, take into account the total personality, and whether it be modern or ancient, use common sense. Be humane, be cheerful and hopeful. I am led to say this because of two groups of patients who have been helped by my conservative methods, my sympathy for the patient and my desire to make life seem worth living for the individual.

Without giving detailed histories, the first group includes those with coronary disorder of the senile or pre-senile period and the second group

includes boys and girls of school age who have cardiac symptoms and findings due to a preceding endocarditis of rheumatoid or of some infectious origin. Illustrative of group one is a man F. aged sixty-seven, weighing about 212 pounds, leading an inactive life in a small community, worrying about his inability to earn a decent living as a merchant and the fact that he cannot get about without having someone at his side every minute of the day "lest something would happen to me." He was told he was in a precarious condition and his wife felt something was bound to happen to him. He described typical angenoid symptoms for which he was given all sorts of remedies including every possible heart stimulant and regulative drug, also codeine and other drugs in full measure. Alcoholic stimulants were prescribed regularly and I am bound to admit were the least harmful of the innumerable prescriptions. Life insurance examinations in which every possible test had been made intensified the conviction that he was doomed. I was able to verify the organic findings, had no reason to doubt the existence of a serious cardiac disorder, but in spite of it all, the heart did its work much better than one would have expected of it, the pulse was regular, there was no cardiac asthma and his systolic blood pressure was rarely above 130—diastolic 70. No doubt he would have fitted into the category of neuro-vascular asthenia or any other name that you choose to give to an organic disorder with the addition of marked functional symptoms.

I have long since stopped predicting death as inevitable in the presence of heart disease, as I also refuse to be alarmed by high blood pressure so long as the renal function is nearly normal. And above all, I refuse to alarm the patient and have him or her know whether the pressure is five or ten points higher or lower. The doctor should know; the patient need not know. The doctor might even stop talking about blood pressure at dinner or other social gatherings.

In the case of the patient referred to, I cut off all medication, diminished and gradually eliminated all sedatives, encouraged him to live on a moderate diet, to reduce weight, to walk up or down stairs quietly, to take moderate exercise, reassuring him about his heart. ("If your heart acted any better, I would send you to a specialist.") The result of all this method of treatment was most satisfactory. Considered a hopeless cripple six years ago, he has been coming of late to my office, unattended, at monthly or bi-monthly intervals. He is now a cheerful individual, more than willing to live on some time longer, thinks life is worth living and is convinced that he has made a real recovery.

My own satisfaction over the patient's progress has been increased by a letter from a distinguished life insurance director (to whom I had expressed my views) that he was in entire agreement with me and that the American Heart Association, through a special committee is investigating coronary disease, that they have addressed a questionnaire to 300 leading specialists in the United States and Canada and that the "findings of the

survey stress a most optimistic view toward coronary artery disease." Spread the good news and let it also include the patients with coronary disease due to an old-time luetic infection. I have in mind another patient, now aged 65, who more than fifteen years ago was frightened out of his wits because of luetic coronary disease. Treated similarly to the other patient, and with due regard to the luetic factor, he has enjoyed fine health these fifteen years or more, and this man too thinks life is worth living, and is ready for another decade if the Lord is willing.

The second group I have in mind comprises children of the pre-adolescent period. This includes boys and chiefly girls between the ages of ten and seventeen, who present marked endo- and myocardial symptoms and who (very properly) are watched very closely as to physical exercise and whose parents are intensely alarmed with forebodings as to what the future might bring—at best a hot house plant, nervous and disgusted that he could not do what other children were allowed to do; no swimming, no dancing, no camp life—just being bored while other children were having lots of fun. In these cases, too, conservatism mixed with a hopeful outlook will help both doctor and patient.

Typical of this group is a fine young girl who came under my care as a child of ten, with marked tachycardia (pulse over 120), pronounced mitral murmur, inclined to obesity (about 106 pounds), no heart enlargement, distinctly anemic, no dyspnea except occasionally after climbing three flights of stairs at a private school. Walking up those stairs was forbidden, but otherwise regular walking exercises were encouraged. Medication was directed solely to control the anemia, to keep down obesity through control of diet and, for a very short period only, moderate glandular treatment. Child and parents were assured that the heart condition would improve as she grew older and that she would be able to hold her own with three older sisters. That child is now a fine young girl of 16 who has retained her cardiac murmurs, has a pulse rate varying from 75 to 80, has done well at school; during the past summer worked in a dentist's office; and has managed to reduce her weight from 190 to 153. Her natural desire for a streamlined figure has been a tremendous stimulus and has led her to adhere to a sensible diet. The medical-care is a very long story in this case, but in the end the principles adopted were a minimum of medication, no more interference with ordinary daily tasks than prudence called for and continuous encouragement to child and parents that she would not be an invalid during the rest of her life.

May I claim in this instance as with a number of similar patients, conservative methods, a minimum of medication, linked with some sober medical judgment have justified the optimism of many years. It may require courage at times and some self restraint; but be an optimist. The patient will be the beneficiary; and the physician will be gratified to know that he has helped to make life more bearable for many a sufferer, old and young.

DR. B. S. OPPENHEIMER'S CONTRIBUTIONS TO POST-GRADUATE MEDICAL EDUCATION

JOSEPH TURNER, M.D.

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Dr. Oppenheimer's long connection with The Mount Sinai Hospital and his valuable services to its patients have gained for him many a well-deserved honor. The Hospital's official files present ample evidence of it; in them one finds ample praise for his services as a clinician on the wards, as an investigator in the laboratories, as the pioneer in developing Electrocardiography in our Hospital, and as a leader in the examination and selection of the house staff. There were other activities in which he took the initiative, but in no endeavor have his efforts been of greater value and permanence or of more far-reaching effects beyond the Hospital's walls than in the field of post-graduate teaching.

While medical instruction in the Hospital goes back many years, it received its greatest impetus in 1923, when, aided by a substantial initial endowment from the late Joseph F. Cullman, post-graduate teaching was formally organized in affiliation with the College of Physicians and Surgeons of Columbia University. Dr. Libman, then Chairman of the Committee on Medical Instruction, supervised the arrangements. Dr. Oppenheimer was one of the first instructors, continuing to give courses up to the time of his retirement from active duty with the staff.

In 1925, he was appointed a member of the Medical Board's Committee on Medical Instruction. He served in this capacity until 1928, when he was appointed Chairman, which post he held until his resignation as Physician to the Hospital in 1939. However, the President of the Hospital, unwilling to relinquish Dr. Oppenheimer's service to this Committee, asked him to continue as a consultant member.

To attempt to describe Dr. Oppenheimer's influence upon the progress of the post-graduate medical instruction in the Hospital would be to write a long and detailed history of the past decade and a half. While space is not available for this, it is, however, desirable to draw attention to a few outstanding events during those years.

Highly significant was Dr. Oppenheimer's success, with the help of Dr. Michael Heidelberger, in persuading Professor Richard Willstatter, of Munich, to come to the United States in 1927, to give the first of the William Henry Welch Lectures in the Blumenthal Auditorium. The names of the distinguished visitors who have given the Janeway and the Welch Lectures in these two decades would fill several pages in a "Who's-

Who" of contemporary medicine. Most of them are Dr. Oppenheimer's friends who came to us at his invitation.

He urged the desirability of publishing, as a Mount Sinai venture, many of the special lectures given at the Hospital, notably those identified with the Janeway and the Welch Lectureships. This was realized when the *JOURNAL OF THE MOUNT SINAI HOSPITAL* came into existence.

Dr. Oppenheimer inaugurated the practice, in 1928, of giving so-called "extracurricular" courses. These were organized apart from the regularly scheduled courses listed in the formal annual catalogue. These "extracurricular" courses were arranged to meet the special needs of certain groups of graduate students which could not be met in the formal program.

It is Dr. Oppenheimer who conceived and carried into practice the program of intensive courses in certain specialties. Notable among these were the four-week courses in Cardiovascular Diseases and similar courses in Gastro-Enterology.

It is difficult to find a yardstick with which to measure the value to the profession and to medical practice of the post-graduate program as it has developed under Dr. Oppenheimer's aegis. Perhaps one method, though somewhat crude, would be to employ the simple statistical summaries which appear in the Hospital's annual records. In 1927, just before Dr. Oppenheimer assumed the chairmanship of the Committee, the graduate students registered in the courses given at the Hospital numbered 125. During the subsequent eleven years, there was a striking increase in the number of registrants, which reached a total of 313 in 1929, Dr. Oppenheimer's last year as Chairman of the Committee.

Here, as well as in other endeavors, Dr. B. S. Oppenheimer displayed an excellent example of what unselfish devotion to a task may accomplish.

RESTING BLOOD FLOW AND PERIPHERAL VASCULAR RESPONSES IN DIFFERENT PORTIONS OF THE EXTREMITIES

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INTRODUCTION

Recent modifications of the venous occlusion plethysmographic method (1 to 4) have afforded a relatively simple approach to the study of peripheral blood flow in man. Since this procedure permits the study of isolated portions of an extremity, it has been possible to obtain evidence which indicates that the nervous control and the responses of the blood vessels are different in the distal as compared with the proximal parts of the limb. The purpose of this paper is to present some of the pertinent observations upon which this view is based and to discuss their significance.

TECHNIQUE

The principle underlying the venous occlusion plethysmographic method was first utilized by Brodie and Russell (5) in determining blood flow through an organ, and was then modified by Hewlett and van Zwaluwenburg (6) for similar measurements in an extremity. It is based on the premise that if venous outflow from a limb is suddenly stopped, the initial rate of increase in limb volume will represent the rate of arterial inflow. The method, in brief, consists of placing a portion of an extremity into a metal container (fig. 1), the opening or openings of which are then made water-tight by means of rubber diaphragms attached to cuffs. The latter are cemented to the skin and the plethysmograph is filled with water maintained at a constant temperature. A collecting pressure (60 to 70 mm. Hg.) is suddenly applied to the extremity proximal to its insertion into the machine (fig. 1 B-1), and the resultant rate of swelling of the limb is recorded on a fast moving drum. Under these conditions, venous outflow is temporarily arrested, while at the same time the effect on arterial inflow is negligible. In order for the rate of swelling of the extremity to be a significant function of true arterial blood flow, it is necessary for the veins to be in a partial state of collapse so that they will offer a minimum of resistance to filling during the initial period following venous occlusion. The calculated readings are expressed as cubic centimeters of blood flow per minute per 100 cc. of limb volume, at a specified room and bath temperature.

PHYSIOLOGICAL CONSIDERATIONS

A. *Resting blood flow.* A marked difference in the rate of resting blood flow in various portions of the extremities was an early observation of workers in this field. For instance, at a room temperature of 25°C. and bath temperature of 32°C., the approximate rate of flow to the finger is 40 cc. per minute per 100 cc. limb volume; to the hand, 9.5 cc.; to the forearm, 1.8 cc.; to the calf, 1.4 cc.; and to the foot, 2.1 cc. Obviously, the great variation in these figures cannot satisfactorily be attributed to differences in the rate of metabolism of the respective tissues. The fact that there are many arterio-venous shunts in the finger-tips and toes and none in the skin of the forearm and leg (7) is probably of importance in this respect, since evidence has recently been obtained which links these specialized

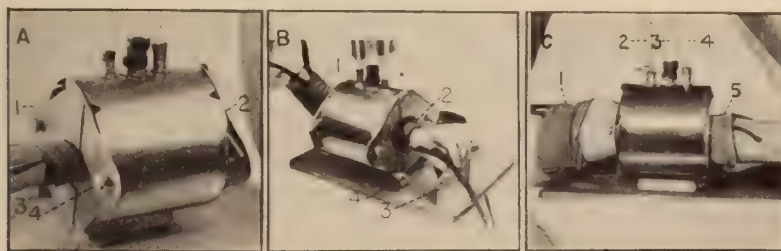


FIG. 1. A. Plethysmograph used to study blood flow in the hand. (1) Leaf o iris diaphragm; (2) one end of apparatus closed off; (3) blood pressure cuff at wrist for producing a venous occlusion pressure; (4) thumb screw for maintaining iris diaphragm in position.

B. Same plethysmograph used to study blood flow in the forearm. (1) Blood pressure cuff for producing a venous occlusion pressure; (2) blood pressure cuff at wrist for maintaining a pressure of 300 mm. Hg. during observations in order to prevent arterial blood flow into and venous return from the hand; (3) support for hand; (4) portion of rubber diaphragm beyond ring.

C. Same plethysmograph used to study blood flow in the leg. (1) Blood pressure cuff for producing a venous occlusion pressure; (2) calibrating burette; (3) wide glass tube; (4) thermometer; (5) blood pressure cuff for maintaining a pressure of 300 mm. Hg. during observations, in order to prevent arterial blood flow into and venous return from the foot. (Reproduced from Ferris, E. B., Jr. and Abramson, D. I., "Description of a New Plethysmograph." *Am. Heart J.*, 19: 233, 1940.)

blood vessels with the processes of temperature regulation (8, 9). The high resting blood flow in the hand under ordinary environmental conditions may, therefore, in great part be due to the need for body heat dissipation, while the much lower rate of flow in the forearm and leg probably is a function solely of the local metabolism of the tissues.

Marked alterations in the basal flow in any one vascular bed can be brought about by changes in the local bath temperature. For example, in the hand, which responds most markedly to this type of stimulus, the average blood flow at a bath temperature of 10° to 14°C. is 2.5 cc. per minute per 100 cc. of limb volume; at 32°, 9.5 cc.; and at 45°, 22.5 cc. Comparable changes occur in the other portions of the extremities.

When the local bath temperature is kept constant and the room tem-

perature altered, changes in blood flow will occur in the hand, while the response in the forearm and leg are not pronounced. For instance, an increase in room temperature from 25°C. to 32°C. will in some instances practically double the blood flow in the hand, leaving that in the forearm and leg only slightly altered. The mechanism responsible for the augmented circulation is similar in some respects to the reflex vasodilatation elicited by the application of heat to distant portions of the body (10), since in both states there is need for greater heat dissipation.

In the case of reflex vasodilatation, moderate warming produces an augmented blood flow in the hand and foot but not in the forearm and leg. Only if the heat is of sufficient intensity to elicit generalized sweating does vasodilatation take place in the latter two regions (9). Sympathectomy

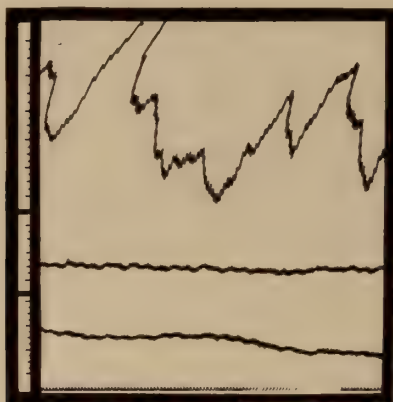


FIG. 2. Spontaneous volume changes at a bath temperature of 32°C. and room temperature of 25°C. Upper curve shows spontaneous variations in hand volume; middle and lower curves represent constant limb volume in the forearm and leg respectively. Time in seconds. Calibrations in 0.25 cc. (Reproduced from Abramson, D. I. and Katzenstein, K. H., "Spontaneous Volume Changes in the Extremities." *Am. Heart J.*, 21: 191, 1941.)

and peripheral nerve block will abolish the reflex vasodilatation in both the distal and proximal portions of the extremities (1, 9, 11, 12). However, the response in the case of the forearm and leg is probably mediated through vasodilator nerves to the skin (9), while that in the hand and foot is elicited by removal of normal vasoconstrictor tonus (1, 11, 12). In this respect it is of interest to note that under ordinary environmental conditions, blocking of cutaneous nerves readily produces a distinct flushing and warming of the skin of the hand and foot, while in the forearm and leg no definite signs of an augmented circulation are apparent (9).

From the above evidence, it can be inferred that a real difference exists in the nervous control of the cutaneous blood vessels in the proximal as compared with the distal portions of the extremities; the skin vessels in the hand and foot being under marked vasomotor control, while those in

the forearm and leg are little if at all affected by nervous vasoconstrictor tonus.

B. *Variations in vascular responses.* In addition to differences in the rate of resting blood flow, there are also differences in the vascular responses in the various portions of the extremities. For example, apparently spontaneous changes in volume are frequently present in the hand, but these are negligible or entirely absent in the forearm and leg (fig. 2). This phenomenon most likely is attributable to variations in the tonus of vessels, particularly those of the venous bed¹ (13). Further, a noxious stimulus (a pinch) or a mental task (a problem in arithmetic) will produce a transient but marked decrease in limb volume in the hand and forearm (fig. 3A).

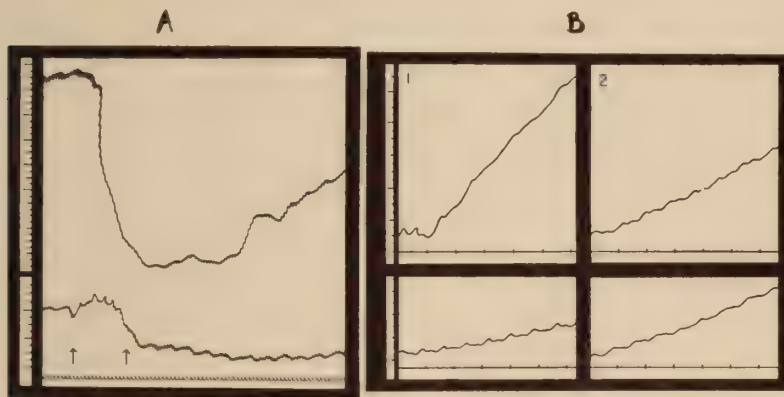


FIG. 3. A. Effect of a pinch on volume of hand (upper graph) and forearm (lower graph). Hand, decrease of 17.3 cc. per liter of limb volume. Forearm, initial rise of 0.8 cc. per liter, followed by a decrease of 3.4 cc.

B. Blood flow changes resulting from mental arithmetic. Upper graph—hand. Lower graph—forearm. (1) Control blood flow. Hand, 12.0 cc. per minute per 100 cc. limb vol. Forearm, 1.4 cc. (2) Blood flow records obtained during the period in which problem was being solved. Blood flow in hand, 5.4 cc. Blood flow in forearm, 2.7 cc. Time in seconds. Calibrations in 0.25 cc. (Reproduced from Abramson, D. I. and Ferris, E. B., Jr. "Responses of Blood Vessels in the Resting Hand and Forearm to Various Stimuli." *Am. Heart J.*, 19: 541, 1940.)

However, the available evidence indicates that the volume change in the hand is the result of vasoconstriction of both the arteriolar and venous beds, while in the forearm, generally only the venous component is involved, the calibre of the arterioles remaining unchanged (14). Should the solution of the mental task be associated with a significant augmentation in systemic blood pressure and pulse rate, then a concomitant increase in blood flow will take place in the forearm as the result of a passive arteriolar dilatation (fig. 3B). The hand, however, will still manifest a decreased inflow, due to arteriolar constriction (fig. 3B), and a transient increased outflow, due to venous constriction.

¹ The venous bed includes capillaries, venules and veins.

Other evidence, supporting the view that the responses of the blood vessels in the extremities vary in the different vascular beds, is the observation that smoking causes a significant decrease in blood flow to the hand but not in the forearm (15); and that epinephrine (8, 16), and voluntary hyperventilation (14) also diminish blood flow to the hand, but at the same time produce a significant augmentation in flow to the forearm. With the latter two procedures, an increase in blood pressure and pulse rate usually accompanies the local response in the forearm. In these instances, as with a mental problem, the systemic changes probably indicate that the altered forearm blood flow is due to a passive vasodilatation, consequent to an increased cardiac output.

It would seem, therefore, that the arterioles of the hand respond to most noxious and psychic stimuli by constricting, while those in the forearm and probably in the leg are either unaffected or even dilate under similar conditions. The finding that with a stimulus, such as a pinch, a decrease in limb volume occurs in the forearm without any change in arterial inflow, indicates that vasoconstriction of the venous bed alone may take place, independently of any other alteration in the vascular tree. In view of this, it is obvious that volume changes in a limb do not necessarily indicate alterations in arterial blood flow.

C. Response to local anoxia. As has already been suggested, the resting circulation in the hand is much greater than that anticipated on the basis of the local metabolism of the tissues alone. Further support for this view has been obtained by studying the response of the blood vessels to local anoxia produced by arterial occlusion (17, 18). In this type of experiment the assumption is made that during the time that blood is prevented from entering the extremity, the tissues incur a blood flow debt which is repaid in the subsequent period of reactive hyperemia. The magnitude of this repayment is, therefore, an indication of the relative metabolism of the tissues. In the case of the hand, the actual repayment is much less than the calculated blood flow debt, while for the forearm and leg both figures are approximately the same. Since the calculated blood flow debt is determined on the basis of the resting blood flow (being the product of the latter and the period of arterial occlusion) it follows that the resting blood flow in the hand is far greater than that actually required by the tissues; the difference representing that portion of the circulation devoted to the function of heat dissipation.

CONCLUSIONS

Certain conclusions can be drawn from the foregoing observations. First of all, since the hand contains arterio-venous shunts which evidently are under the marked control of the vasomotor center, the vascular responses in this region cannot be considered as representative of peripheral blood flow generally. Further, in contrast to the vascular responses in the hand,

the blood flow to the normally innervated forearm and leg is more constant, not being diminished, at least, by most noxious stimuli. The arterioles in both types of vascular beds actively dilate for the purpose of heat dissipation, but differ in that those of the hand function under ordinary conditions, while those of the forearm and leg are affected only when the need is excessive. The vascular beds in the forearm and leg, therefore, are more satisfactory than the hand for studying the local effect of sudden changes in the systemic circulation. Finally, they are probably more truly representative of peripheral blood flow as it relates to the metabolic needs of the extremities.

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ACUTE GENERALIZED POSTOPERATIVE PERITONITIS SIMULATING CORONARY ARTERY OCCLUSION

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Suddenly appearing shock with rapid thready pulse, muffled heart sounds, marked drop in blood pressure, and pain in the chest or upper abdomen, readily suggests the diagnosis of coronary artery occlusion. That the protean variations of this clinical syndrome may simulate a variety of subdiaphragmatic conditions such as acute pancreatitis, acute cholecystitis, or perforated gastric or duodenal ulcer is a familiar observation. Physicians generally are alert to the possible consequences of such a serious diagnostic error. With the more widespread application of the electrocardiograph, difficulty and confusion in diagnosis are encountered much less frequently.

There is, however, too great a readiness to make the diagnosis of postoperative coronary artery thrombosis, particularly in shock states appearing suddenly. Herrick (1) in a timely paper entitled "On Mistaking Other Diseases for Acute Coronary Thrombosis" lists many conditions frequently wrongly diagnosed as coronary artery occlusion. Bean (2) likewise comments on "the frequency with which this diagnosis is now uncritically made when, in fact, some other disease is responsible for the symptoms." It is the purpose of this paper to report two cases in which a rapidly spreading postoperative peritonitis produced the clinical picture of sudden shock which was erroneously attributed to occlusion of a coronary artery and to discuss the diagnostic difficulties presented by such cases.

CASE REPORTS

Case 1. History (Adm. 371271). L. P., a woman aged 69, was admitted to the hospital for operative resection of a neoplasm of the splenic flexure. In the year previous to the onset of symptoms she had had a period of hospitalization in another institution. During that stay, an empyema of the gall bladder had been drained with subsequent complete recovery. An electrocardiogram at that time showed evidence of myocardial involvement presumably due to coronary artery sclerosis. Dyspnea upon exertion was the only symptom possibly referable to the heart, but this was attributed to emphysema and obesity rather than to myocardial insufficiency.

Examination. The patient was an obese, elderly woman with a moderate secondary anemia. The lungs were emphysematous. The heart was not enlarged and the cardiac sounds were of good quality. The blood pressure was 160 systolic and 85 diastolic. There was a large nodular mass in the left upper quadrant of the abdomen, which by previous x-ray study had been determined to be a neoplasm of the splenic

flexure. After preliminary transfusions, the surgeon performed an externalization of the intestinal loop containing the carcinoma and the operation was terminated.

Course. Although additional transfusions were successful in combating the immediate postoperative shock, the patient's course during the next four days was characterized by fever of 102° to 103°F., rapid pulse, and abdominal pain. The exposed section of colon ruptured spontaneously at the site of the carcinoma and intestinal contents drained into the dressings. On the fifth day after operation, the patient suddenly went into collapse. The heart sounds became inaudible, the pulse was hardly perceptible and extremely rapid. The breathing was rapid and shallow, a cyanotic pallor and profuse perspiration appeared, and the blood pressure dropped. No change in the abdominal signs was noted. The temperature rose, the patient entered a deepening stupor, and in twelve hours she died. Death was considered due to acute coronary artery thrombosis. Pulmonary artery embolus was also suggested to explain the sudden shock state. As has been pointed out, this may give rise to a similar clinical picture (3).

Relevant Necropsy Findings. In the center of a one-foot length of exteriorized splenic flexure there was a quarter-size opening at the site of the carcinoma through which semi-fluid fecal material escaped. On separating the intestinal loop from the wound edges, a wide drainage tract was found to extend upwards to the left sub-phrenic space where several hundred cubic centimeters of thin brown fluid had accumulated. This same thin fecal fluid was also found lying between the loops of small intestine. The entire visceral and parietal peritoneum was dull and covered with a fine fibrinous exudate. The lungs and pulmonary vessels showed no significant abnormalities.

The heart was small with moderate dilatation of the chambers. There was slight calcification of the posterior mitral leaflet and of the sinus of Valsalva. The coronary arteries were patent and showed moderate intimal thickening. The myocardium was flabby but showed no recent infarctions.

Summary. 1) Carcinoma of splenic flexure with externalized carcinomatous loop and rupture of the carcinoma. 2) Acute generalized fecal peritonitis with left subphrenic loculation. 3) Parenchymatous degeneration of viscera. 4) Coronary sclerosis, mild, without narrowing.

Comment. The course of events became clear after the post mortem examination. There had first developed a localized intra-abdominal (sub-phrenic) collection of purulent material with fairly circumscribed peritonitis, resulting from the flow of intestinal contents through the wound into the abdomen from the ruptured carcinoma. On the fifth day, there was a sudden extensive spread of peritoneal infection with rapidly ensuing collapse. The patient was elderly and had had previous electrocardiographic evidence of coronary artery disease. The shock-like clinical picture of the final episode was similar to that seen so frequently in acute coronary artery thrombosis. The absence of pain in a very sick patient with the usual variety of postoperative complaints was not incompatible with the suggested diagnosis of coronary artery occlusion. An electrocardiogram might have been helpful, but unfortunately was not done.

Case 2. History (Adm. 429230). S. S., a woman, aged 59, complained of recurring attacks of upper abdominal pain relieved by food. Although a gastro-intestinal x-ray had been reported to be normal six months before, because of significant weight loss and persistent pain she was admitted to the hospital for study.

Examination. The patient was chronically ill. Her heart was normal according to the usual clinical examination. The lungs were clear. The blood pressure was 145 systolic and 80 diastolic. There was a positive guaiac test for blood in the stools. Roentgen examination of the stomach now revealed a carcinoma. This finding was confirmed by gastroscopy. The electrocardiogram showed normal sinus rhythm with left ventricular preponderance, and a low amplitude of the QRS complex in lead II. These changes were not considered abnormal in a patient of this age.

At operation under avertin and ethylene anesthesia a subtotal gastrectomy with anterior gastro-jejunostomy was done. During the operation, bleeding from the pancreas was encountered which was readily controlled by pressure packing.

Course. Directly after operation, the temperature rose to 102°F., and the pulse rate became rapid, ranging from 100 to 120 per minute. There were no significant signs in the lungs, nor any abdominal signs except moderate intestinal distension for which an enema was given. Following the enema the patient became cyanotic and her face had an ashen gray hue. The blood pressure fell to 90 systolic and 70 diastolic. The heart rate was accelerated to 160 per minute and the cardiac sounds were only of fair quality. Profuse sweating occurred, the pulse became poor and the patient presented the typical clinical picture of shock. There was no abdominal tenderness, no signs of ascites, nor any other evidence to suggest an intraabdominal infection or hemorrhage.

A diagnosis of coronary artery occlusion was suggested as an explanation for the state of shock. An electrocardiogram showed tachycardia and somewhat lower T waves in leads I and II than previously, minor variations from the original electrocardiogram and not typical of acute myocardial change. Fever persisted, also shock and intermittent complaints of substernal oppression. A few hours before death the abdomen became tender and abdominal aspiration gave clear evidence of a peritonitis. The respirations became rapid and labored, the cardiac rhythm became irregular, and she went into coma and died.

Relevant Necropsy Findings. Partial dehiscence of duodenal stump; acute diffuse fibrino-purulent peritonitis; coronary sclerosis without narrowing; and acute interstitial myocarditis (microscopic).

Comment. Because of its anatomical location, the duodenal stump is closed frequently only with the greatest difficulty in subtotal gastrectomy. The suture line is immediately thereafter subject to tension and to the action of the digestive juices. For these reasons, dehiscence of the stump is unfortunately encountered in a certain number of cases. The leakage of intestinal contents sets up first a localized peritoneal reaction, and, if rapidly diffused, involves the entire peritoneal surface, at times with a rather suddenly induced picture of shock. Such was the sequence of events in this case. Initially there was a localized peri-duodenal exudate which extended into the general peritoneal cavity causing the clinical syndrome described. Perhaps some clue to the presence of an intra-abdominal complication might have been derived from the immediate postoperative tachycardia (100 to 120 beats per minute) yet, this could readily be the normal accompaniment of the febrile reaction of 102°F. frequently seen for a day or two after any uncomplicated but extensive operation. There were no signs of peritonitis until a few hours before death. Although the electrocardiogram showed no typical changes of myocardial infarction, the occurrence of sudden collapse in a middle aged woman directly after the

exertions of the use of an enema, where no other cause could be discovered, suggested a presumptive diagnosis of coronary artery occlusion.

DISCUSSION

Following extensive intra-abdominal surgical procedures, patients frequently manifest such signs as fever, dyspnea, cyanosis, and tachycardia and there may be cough, vomiting, cardiac arrhythmias, chest or abdominal pain. In the great majority of cases these symptoms are part of a postoperative reaction resulting from the necrosis or repair reaction of incised tissues, or from the "stirring up" of infected areas or neoplastic tissue. Usually such phenomena disappear spontaneously in a few days unless complications such as pneumonia or peritonitis ensue. It is during the immediate postoperative period, however, that at least half the instances of postoperative coronary thrombosis occur. When it is remembered that the most distinctive symptom of coronary artery occlusion, substernal or precordial pain, is usually absent or of minimal intensity under such conditions and that other signs of coronary occlusion, i.e., fever and leucocytosis, are masked by and confused with the signs of postoperative reaction, it becomes clear why the diagnosis of coronary occlusion may be extremely difficult. This difficulty becomes even greater when the patient goes into shock. In this state the blood pressure drops, the heart sounds become feeble and the pulse fails. Pallor or cyanosis may be present and the respirations become rapid and shallow. This clinical picture surely suggests acute coronary occlusion. Pain is the only important symptom lacking to complete the classical picture, and as mentioned before, absence of pain is frequent in postoperative coronary occlusion.

Gorham and Martin (4) analyzed the clinical histories of 100 cases of coronary occlusion proved by necropsy and noted that 42 of these patients had had no pain in their attacks. The bibliography appended to their paper lists numerous reports of similar observations with an incidence of painless coronary occlusion ranging from 38 to 61 per cent. Bean (5) in a statistical review of 189 cases of myocardial infarction, found pain had occurred in no more than 72 per cent of the acute attacks. He refers to numerous other reports of painless acute coronary occlusion, a syndrome which has now received general acceptance. Master, Dack, and Jaffe (6) in their study of 35 cases of postoperative coronary occlusion, noted pain in only two-fifths of the cases and in these, the pain was often slight.

It is clear, therefore, that on purely clinical grounds, it is extremely difficult in the postoperative period to determine whether or not a suddenly ensuing shock state has been caused by an acute coronary artery occlusion. It becomes necessary, therefore, to obtain information from the electrocardiogram. It must be emphasized that for an accurate interpretation of postoperative electrocardiographic changes it is essential to know the pre-

operative electrocardiographic pattern. Pre-existing myocardial involvement may have so altered the electrocardiogram that superimposed acute changes present an atypical picture. Doubtful cases, however, may often be clarified by serial electrocardiograms. In patients, over fifty, with or without a cardiac history or clinical evidence of heart disease, upon whom an extensive surgical procedure is contemplated, (particularly intra-abdominal-surgery) a preoperative electrocardiogram is extremely important and should be a routine procedure.

No attempt will be made to discuss the etiological relationship between postoperative coronary thrombosis, the operative procedure, and the postoperative course. Before more is known about the mechanism of thrombosis, such considerations can be only speculative. Warning must be given against the fallacy of linking two events causally merely because of their temporal juxtaposition. Elderly people may develop coronary occlusion or other cardiovascular accidents at any time. Recently a sixty-three year old hypertensive patient was admitted to a surgical service for excision of a mammary duct papilloma. There was no evidence of heart disease. Before the operation could be begun and before anesthesia was administered, the patient complained of chest pain which was considered to be an attack of angina pectoris. It was thought wise to defer the operation and the patient was sent to the ward. After a symptom-free interval of a few hours, she complained of the chest pain again, and died in a few minutes. Autopsy revealed the cause of death to be hemopericardium with cardiac tamponade from a rupture of the ascending aorta due to medial degeneration. If the anesthesia had been begun or if the operation, minor as it was to be, had been completed, this death too, would have been designated as a postoperative event. Furthermore, without an autopsy, the clinical diagnosis of coronary artery thrombosis would have been maintained, illustrating again how the classic syndrome of coronary artery occlusion may have another anatomical basis.

SUMMARY AND CONCLUSIONS

The clinical picture of acute coronary artery occlusion may be stimulated by many other supra- and infra-diaphragmatic syndromes. There is a general awareness of this problem in differential diagnosis. Further emphasis, however, is required in connection with postoperative shock states which are too uncritically ascribed to acute coronary artery occlusion. Two cases of a rapidly spreading postoperative peritonitis accompanied by peripheral collapse and the clinical picture of shock are described. A diagnosis of acute coronary occlusion was made in each instance. Autopsy failed to disclose such a condition in either case. The clinical peculiarities of postoperative coronary thrombosis are commented upon and it is urged that definite confirmatory evidence be sought before making this diagnosis

postoperatively in shock states. The value of the preoperative electrocardiogram as a basis of comparison for postoperative records is stressed.

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BROWN-SEQUARD SYNDROME IN ASSOCIATION WITH TUBERCULOUS SPONDYLITIS AND PULMONARY SILICO-TUBERCULOSIS

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A Brown-Sequard syndrome is met with very often in association with tumor of the spinal cord or with syphilis of the spinal cord; occasionally it is the result of trauma, or of hematomyelia. The case to be reported here illustrates a relationship of Brown-Sequard syndrome to tuberculous spondylitis (caries of the spine).

CASE REPORT

History. The patient, Harry H., age 56, a stone cutter by occupation, was referred to the neurologist of the Johns Hopkins Hospital, Dr. Frank R. Ford, because of "weakness of the right leg and a general run-down condition." The family history threw no light upon the patient's illness. The parents were long-lived persons and there was no history of tuberculosis, cardiovascular disease, goitre, or neuropsychiatric disease in the family. The patient was married but had had no children. In childhood the patient had had mumps, measles, whooping cough and chicken pox. Eight years before admission while at heavy stone work he ruptured himself and had worn a truss since that time. About four years prior to admission a wound resulting from a cut on his hand became infected; he developed high fever and was forced to undergo treatment in a hospital for two weeks.

Though the patient had been exposed to stone dust over a period of many years, he dated the onset of his illness to the infected wound for which he had been hospitalized four years previously. Soon after leaving the hospital on that occasion he noticed that his right leg dragged on walking and that there was occasional jerking in the muscles of that leg at night. The right lower extremity had been weaker than the left ever since. During the four years prior to admission the patient had lost twenty-five pounds in weight, and had complained of lack of appetite and of increasing general weakness.

One month before admission he began to suffer from a troublesome cough (without much sputum) and was sent to a hospital in Washington County, Maryland where, after examination, the physician in charge advised him to consult Dr. Ford. It was later learned that he had had some edema of the ankles, especially on the right side, occurring toward evening for at least two years. He had also become short of breath on exertion and had had to rise at night from two to four times to pass urine.

Examination. Temperature, 101.6° F. Pulse rate, 136 per minute. Respiratory rate, 20 per minute. Blood pressure, 130 systolic and 90 diastolic. Height, five feet eight inches; weight, 123 pounds 31 pounds below calculated ideal weight. Slight pallor was present. The right lower extremity was cooler than the left. Slight edema of the ankles was present on admission, but soon disappeared after rest in bed. There was a slight enlargement of the retrocervical lymph glands and in each axilla there was one non-tender gland the size of a marble. There was slight deafness

in both ears. The tonsils were small, apparently not infected. The trachea deviated somewhat to the right of the middle line. The thyroid gland was negative.

During respiration the right side of the chest expanded somewhat less than the left. There was slight dulness over the right upper and right lower lobes. Moist râles were heard at the right apex and at both bases after coughing.

The apex beat of the heart was 9 cm. to the left in the fifth intercostal space. Marked tachycardia was noted; a diffuse pericardial friction rub was audible. There was palpable thickening of the peripheral arteries, especially the brachials.

The abdomen was not tender; the liver edge was firm and easily palpable at about the level of the umbilicus; the spleen was not palpable. Genitalia were normal.

On neurological examination, there was definite weakness of all muscles of the right lower extremity and of the right side of the abdomen. The right lower extremity was much colder than the left and exhibited marked spasticity with patellar clonus, ankle clonus and exaggeration of the deep reflexes. Muscular strength in the left lower extremity did not seem to be impaired but the deep reflexes were active and there was a positive Babinski sign on the left as well as on the right.

On testing sensation, there was outspoken analgesia with thermo-hypoaesthesia over the left lower extremity and over the trunk as high as a level a little above the umbilicus. Pain and temperature senses were normal in the right side of the body. Vibratory sensations were diminished in the right lower extremity. There was a narrow band of anaesthesia about the trunk on the right side just above the umbilicus.

Laboratory Data. Blood: red blood cells, 4,300,000; hemoglobin, 86 per cent, white blood cells, 6,040, with a relative increase of the large mononuclear elements, 18 per cent; Wassermann reaction negative; blood sugar, 125 mg. per cent; non-protein nitrogen 26 mg. per cent; carbon-dioxide combining power, 49.4 volumes per cent. Urine: Specific gravity, 1020; slight albuminuria; no sugar; no casts; no bile; no diacetic acid. Sputum: Smears thus far studied revealed no tubercle bacilli, though cutaneous tuberculin tests yielded rather strongly positive results. Cerebrospinal fluid: On lumbar puncture, no evidence of block could be elicited; there was no xanthochromia; the cell count was not increased, and the Pandy test was negative. Roentgenograms: X-ray examinations of the spine revealed changes in the thoracic area from the fourth to the eighth thoracic vertebra, probably tuberculous. In this area there was kyphosis with some angulation. On x-ray examination of the lungs, there was very marked spotty involvement throughout both lungs; in the right lower lobe there were some larger areas of consolidation but no definite evidence of cavitation could be discovered. The x-ray pictures of the lungs were strongly suggestive of advanced pneumoconiosis (pulmonary silicosis) with probable superimposed pulmonary tuberculosis to which the fever of the patient was attributed.

DISCUSSION OF THE NEUROLOGICAL LESIONS

As to the localization of the lesion in the transverse section of the spinal cord, it was obvious that the paresis of the muscles of the right lower extremity and right abdomen, accompanied by exaggeration of the deep reflexes with ankle clonus, patellar clonus, and positive Babinski sign on the right, pointed to involvement of the right pyramidal tract. The impairment of deep sensation on the right suggested involvement of the right posterior funiculus, while the radicular zone of anaesthesia on the right suggested a lesion of the posterior root. The coldness of the right lower extremity was probably due to involvement of the descending vaso-constrictor fibres in the lateral column on the right side.

The analgesia and thermo-hypoaesthesia of the left lower extremity and of the trunk as high as two inches above the umbilicus pointed to involvement of the spino-thalamic tract (Gower's tract) in the right lateral column.

The positive Babinski sign on the left with some exaggeration of the deep reflexes in the left lower extremity pointed to slight involvement of the left pyramidal tract.

As to the localization of the lesion in the longitudinal plane, the disturbances of motility pointed to involvement of the pyramidal tracts of both sides (much more marked on the right than on the left) somewhere in the thoracic cord.

Disturbances of sensibility, however, permitted precise localization at the level of the eighth thoracic segment of the spinal cord (corresponding to the level of the fifth thoracic spinous process).

It was evident, therefore, that there was an incomplete transverse lesion of the spinal cord at the level of the eighth thoracic segment, involving the posterior root and the posterior and lateral columns on the right at that level and, to a very slight extent, the pyramidal tract in the left half of the cord probably at the same level.

This incomplete transverse lesion had given rise to a somewhat atypical Brown-Sequard syndrome including 1) a zone of radicular anaesthesia (posterior root of eighth thoracic nerve); 2) right hemiparesis below the level of T-8; 3) slight bathyanaesthesia on the right; and 4) outspoken analgesia and thermo-hypaesthesia on the left, complicated, however, by 5) slight involvement of the pyramidal tract on the left.

Nature of the Neurological Lesion: Since the Brown-Sequard syndrome is most common in association with tumor of the spinal cord or with syphilis of the cord, it was important to rule these out. Syphilis was excluded by the negative blood Wassermann reaction and by the negative findings in the cerebrospinal fluid.

Tumor of the spinal cord is so often overlooked that the possibility of its existence was carefully considered in this patient. The absence of pain, however, throughout the whole course of the disease was strongly against the existence of tumor since pain (either root pain, column pain, or back pain) is the first symptom in about 90 per cent of all cases of tumor of the spinal cord, whether intramedullary or extramedullary. In 17 per cent of the cases of tumor of the cord there is retention of urine in the early stage but the only bladder disturbance complained of by this patient was occasional nocturia. The findings on lumbar puncture also militated against this diagnosis since the hydrodynamic relations seemed to be normal, the Queckenstedt test did not show evidence of block, and the cerebrospinal fluid was not xanthochromic, did not contain protein, and showed no increase in cells.

It seemed, therefore, plausible to connect the partial transverse lesion of the cord with the tuberculous spondylitis which caused either a compression myelopathy (without block in the cerebrospinal fluid) or interfered with the

blood supply at the level of the eighth thoracic segment with resulting partial myelomalacia.

Diagnosis: As a result of the diagnostic study it was decided that we had to deal with:

1. Spondylitis tuberculosa (caries of the spine) with kyphosis and angulation leading to an incomplete transverse lesion at the level of the eighth thoracic segment of the spinal cord with a somewhat atypical Brown-Sequard syndrome.
2. Advanced silico-tuberculosis of the lungs with characteristic x-ray findings and with continuous fever.
3. Myocardiopathy with tachycardia, pericarditis, and hepatomegaly (chronic passive congestion) secondary either to interference with the pulmonary circulation by the silicosis or to arteriosclerosis.
4. Secondary anemia (red blood cells, 4,300,000; hemoglobin, 86 per cent).
5. Undernutrition (31 pounds below calculated ideal weight).

Treatment: As the pulmonary tuberculosis seemed to be active with continuous fever and troublesome cough, it was decided to combat the tuberculous process by complete rest in bed and general upbuilding. As the lesion in the spinal cord had not been progressive early operative interference in the treatment of the tuberculous spondylitis need not be undertaken, though the spine will be immobilized by the hospital orthopedist.

The patient will be given an abundant diet with large quantities of proteins, carbohydrate, vitamins and fats (including cod liver oil). It is possible that a rapid gain in weight and a better appetite can be induced by injecting daily doses of from five to ten units of protamine zinc insulin twenty minutes before breakfast and twenty minutes before the evening meal; there need be no fear of causing a hypoglycemia through the use of the insulin since the patient's blood sugar is high (125 mg. per cent).

The myocardial weakness with chronic passive congestion is an indication for chronic digitalis therapy. The secondary anemia can probably be overcome by the general upbuilding measures and by the administration of ferrous sulphate three times daily.

If under treatment the temperature returns to normal, the heart becomes compensated, and weight is gradually gained, consideration may later on be given to the possibility of benefiting the patient further by surgical intervention upon the spine.

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THE SIGNIFICANCE OF NEGATIVE T WAVES IN ALL THREE STANDARD LEADS OF THE ELECTROCARDIOGRAM

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When one has taught that the proper method of clinical electrocardiographic research is the study of electrocardiograms obtained from cases which later had been well studied in the pathologic laboratory, it may seem paradoxical to present work in which an attempt is made to correlate electrocardiograms with clinical diagnoses. Our justification lies in the fact that in many cases in which the classification of cardiac disease appeared clear-cut on clinical grounds, it was never possible to have contemporary pathologic study. Universal T wave negativity has long been known in electrocardiograms and examples are readily found in many of the standard texts of electrocardiography. We have noted particularly the occurrence of negative T waves in the three standard electrocardiographic leads in cases in which there were one or more attacks of acute coronary occlusion and in cases in which there was severe coronary disease as manifested by angina pectoris but without the history of acute occlusion and following administration of digitalis. However, it was the recurring observation of negative T waves in all three standard leads in cases of recovering acute pericarditis and in chronic pericarditis that prompted this study of a large series of electrocardiograms having as a characteristic negative T waves in all three derivations.

In many instances these electrocardiographic pictures have been enigmatic, particularly where multiple factors, as hypertension, valvular disease, coronary disease, metabolic disorders and digitalis, might be operative. Under such circumstances it is often impossible to assess accurately the effect on the electrocardiogram of any particular factor when combined with other conditions known to be capable of producing electrocardiographic changes. It would be erroneous to study on a statistical basis the material we have investigated, as clinical diagnoses lack the necessary exactitude. We do not believe a scientific method need end necessarily in exact numerical results and think that from our material we have extracted general truths which will prove helpful in the clinical interpretation of electrocardiograms.

The material consisted of electrocardiographic tracings of 435 patients who showed at one time or another negative T waves in all three derivations of the standard electrocardiogram.

The tracings were first grouped according to the nature of the QRS com-

plex (table 1). The peculiarity of the normal human electrocardiogram with the potentials of depolarization and repolarization giving rise to deflections in the same direction has often been commented on. It so happens that the majority of our tracings in which there is universal T wave negativity have the QRS complex upright in all three leads. Interestingly enough, many of the tracings resemble the most stable type of electrocardiogram in the dog, in which the T wave may be negative and the QRS upright in all three leads. A few instances of bundle branch block with upright QRS complexes and deeply inverted T waves in all three leads have been encountered, again similar to one pattern of bundle branch block in the dog. It has been of interest to note that ventricular extrasystoles may occur with the same type of upright QRS and negative T waves in all three leads. In rare instances in these latter types of abnormal electrocardiograms we have observed a refutation of Einthoven's law as applied to the T waves and we are in accord with the view of Wolferth

TABLE 1

Nature of the QRS complex in electrocardiograms in which the T waves in all three standard leads were negative

ELECTROCARDIOGRAMS SHOWING	CASES
QRS complex upright in all three standard leads.....	279
Left axis deviation.....	111
Right axis deviation.....	9
Miscellaneous types of QRS complexes including intraventricular conduction disturbances and large S waves in various leads.....	36
Total	435

and his co-workers that the left arm cannot always be considered as leading from the peripheral electric field of the heart. We had noted previously that in cases of acute pericarditis the elevation of the RST segment might be greater in lead I than in lead II when that in lead III was isoelectric.

It is seen (table 2) that severe essential hypertension is often the clinical diagnosis in cases in which there are negative T waves in all three leads and the QRS complexes are upright (fig. 1). The blood pressure in this group usually approximated 250 mm. of mercury systolic and 125 diastolic. That cases of aortic stenosis should be placed so prominently in this list has been to us an interesting finding. In these electrocardiograms there was generally a moderate depression of the ST segment in lead I, often sloping in character, and sometimes there was depression of the ST segment in all three leads, in which case it was maximal in lead II. In occasional instances there was no significant depression of the ST segment in any of the three leads.

The incidence of pericarditis in this group is of importance but a not

unexpected observation. The miscellaneous cases in this group, included the following clinical diagnoses: normal hearts by clinical examination, digitalis medication, hyperthyroidism and degenerative heart disease, uremia, myxedema, paroxysmal tachycardia, chronic bronchitis, emphysema and degenerative heart disease, digitalis with combined valvular and hypertensive disease, arteriosclerotic heart disease and various combinations of these conditions.

When the electrocardiograms showing T wave negativity in all three leads and left axis deviation are studied (table 3), it may be seen that they are drawn mainly from patients having severe essential hypertension. The miscellaneous cases in this group consisted of degenerative heart disease, various forms of hyperthyroidism in the older age groups, associated val-

TABLE 2

Conditions showing electrocardiograms with negative T waves in all three leads and upright QRS complexes

CLINICAL DIAGNOSIS	AGE, YEARS			TOTAL
	40 and less	40-55	55+	
Aortic valvular disease (stenosis component predominant).....	6	21	10	37
Combined aortic and mitral disease.....	1	7	2	10
Severe essential hypertension—B.P. more than 200/110.....	24	30	19	73
Essential hypertension and coronary sclerosis.....	1	12	18	31
Coronary sclerosis (angina pectoris).....	0	7	9	16
Coronary sclerosis and myocardial infarction (history of acute coronary occlusion) ..	0	12	10	22
Pericarditis.....	14	4	1	19
Miscellaneous.....	11	21	39	71
Total.....	57	114	108	279

vular and coronary disease, chronic nephritis and combinations of these conditions, sometimes confused in part by digitalis medication (figs. 2 and 3).

There were only nine instances encountered in which the T waves were negative in all three leads and right axis deviation was present. In four cases the diagnosis was recent coronary occlusion and there was one case each of coronary sclerosis and angina pectoris; coronary sclerosis with angina pectoris and the history of an ancient acute coronary occlusion; recurrent pulmonary emboli; mitral stenosis; and mitral stenosis under digitalis therapy. In all of the nine instances the blood pressure was in the low normal range and the two patients that had mitral stenosis were more than forty years of age.

In the group of thirty-six cases in which there were various types of

QRS complexes the majority had intraventricular conduction disturbances, usually of the type with the QRS complex upright in all leads. One in-

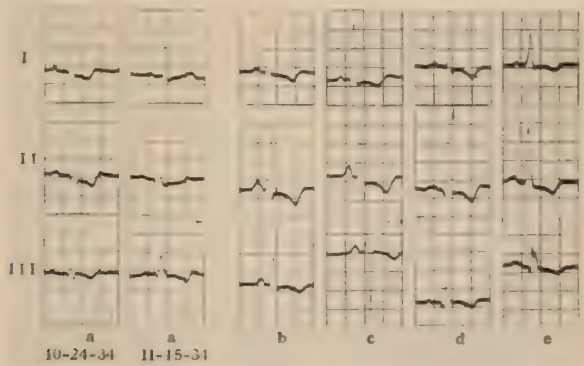


FIG. 1. Electrocardiograms with negativity of the T waves in the three standard leads in conditions causing increase of work of the left ventricle.

- a. Severe hypertension (260 mm. of mercury systolic and 140 diastolic) in a man forty-three years of age who had an apparently normal sized heart, and in the second tracing a return toward normal following rest in bed and extensive sympathectomy.
- b. Severe hypertension in a man forty-five years of age who had recurring cerebrovascular accidents but no cardiac symptoms. (The concordant type of left ventricular strain pattern.)
- c. Severe hypertension in a man forty-six years of age who had diminished cardiac reserve, early renal insufficiency and hypertensive retinitis.
- d. Aortic stenosis in a man thirty-eight years of age who had moderate cardiac enlargement.
- e. Aortic insufficiency in a man fifty-eight years of age who had moderate cardiac enlargement.

TABLE 3

Conditions showing electrocardiograms with negative T waves in ^a three leads and left axis deviation

CLINICAL DIAGNOSIS	AGE, YEARS			TOTAL
	40 and less	40-55	55+	
Aortic valvular disease.....	0	3	1	4
Severe essential hypertension.....	8	24	18	50
Essential hypertension and coronary sclerosis (angina pectoris).....	0	4	7	11
Essential hypertension and coronary sclerosis (history of acute coronary occlusion).....	1	2	5	8
Coronary sclerosis (angina pectoris).....	0	1	2	3
Coronary sclerosis (history of acute coronary occlusion).....	0	2	5	7
Miscellaneous.....	4	9	15	28
Total.....	13	45	53	111

stance occurred in which the QRS complex was downward in all leads. In other cases there were large S waves in all three leads, or a markedly tri-

phasic QRS in lead III or, in a few instances, the type of QRS complex described in detail by Sodeman and Engelhardt in which there is a deep S_3 , and R_2 is greater than R_1 . In these cases the clinical diagnosis usually was hypertensive and coronary heart disease with an occasional case of coronary sclerosis without hypertension and of other combined types of heart disease in elderly patients.

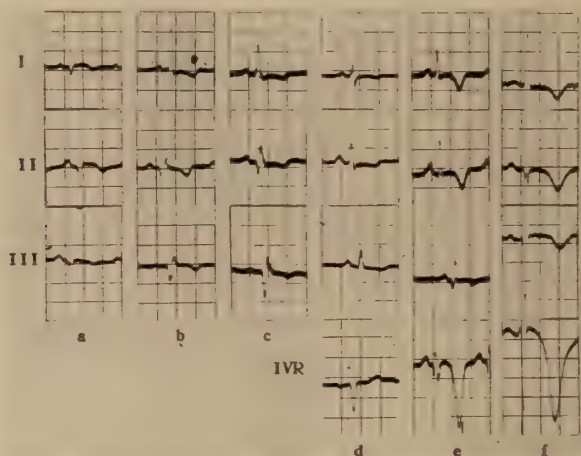


FIG. 2. Electrocardiograms with negativity of the T waves in the three standard leads from patients suffering from coronary disease.

a. Recovery period from acute coronary occlusion in a man sixty-nine years of age. This type of tracing was still present nine months later but three years later there were left axis deviation and a T_1 pattern.

b. Coronary sclerosis and angina pectoris in a man fifty-eight years of age who gave the history characteristic of coronary occlusion two years previously.

c. Coronary sclerosis and angina pectoris in a woman fifty-two years of age who gave the history suggestive of acute coronary occlusion five years and again more definitely one month previously.

d. Coronary sclerosis in a man of fifty-three years of age whose clinical disease ran a rapid course over a few months with progressively severe anginal attacks but without any attack or episode to suggest an acute coronary occlusion. At necropsy the heart weighed 540 gm. and there were marked dilatation of the left ventricle, coronary sclerosis of a severe degree and multiple small myocardial infarcts. Small pulmonary emboli and areas of pulmonary infarction were also present.

e. History characteristic of coronary occlusion one month previously. The patient was a man fifty-five years of age.

f. History characteristic of coronary occlusion a day previously in a woman seventy years of age who had had known hypertension for five years.

Altogether there is a group of twelve patients, all of whom were less than fifty-five years of age and five of whom were less than forty years of age and in whom the results of cardiovascular investigation were completely negative except for the abnormality of the electrocardiograms (fig. 4). In two cases the inversion of the T waves occurred after paroxysmal tachycardia and in one case during a time when multiple ventricular extrasystoles were occurring. In one case, marked obesity was present. In four cases forms of psychoneurosis were present, with circulatory symp-

toms of functional character. These cases are believed to be similar to the cases described by Graybiel and White (2 and 3) in which the electrocardiogram showed negativity of T_1 or T_2 in the absence of any apparent structural disease of the heart. These authors have also pointed out that deviation of the T waves from usually accepted normals may occur in hyperthyroidism and after paroxysmal tachycardia. Pardee stated that negativity of T_1 has not been seen in cases of neurocirculatory asthenia but two of our cases in which there was negativity in this lead as well as in leads II and III might be classified with this diagnosis. In two cases the electro-

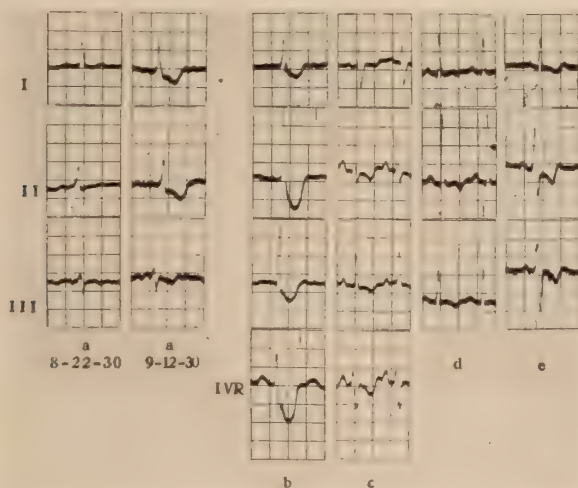


FIG. 3. Electrocardiograms showing negative T waves in the three standard leads from a miscellaneous group of conditions.

a. Effect of digitalis in a patient of seventy-four years who had degenerative heart disease and auricular fibrillation.

b. Striking effect of digitalis in a patient of thirty-six years who had rheumatic heart disease with both aortic and mitral endocarditis.

c. Recurring pulmonary emboli in a girl of seventeen years who had chronic ulcerative colitis. Necropsy showed the presence of pulmonary emboli and the heart was normal to gross and histologic examination.

d. Exophthalmic goiter in a man of thirty-nine years, whose heart was believed structurally normal.

e. Taken during a spontaneous attack of angina pectoris in a man forty years of age. An electrocardiogram, taken two days previously, had been normal.

cardiogram spontaneously returned to normal within a day's time, in one case it became normal with exercise and in another it approximated normal after administration of atropine. In all of the electrocardiograms in this group the T waves were never deeply inverted and never had the characteristic cove-plane shape so characteristic of the relic of ancient myocardial infarction.

In a few instances we have wondered whether unrecognized pericarditis in early life might have a relic in the electrocardiogram in adulthood. Not included in this group of twelve cases was a man thirty-five years of age

whose electrocardiogram is reproduced (fig. 4e) and in whom we believe the bird shot, received in a shotgun accident when he was eleven years of age and demonstrated roentgenoscopically as probably being in the pericardium, may have played a role in a pericardial reaction and the electrocardiographic abnormality.

The electrocardiographic picture of pericarditis has been well described and in particular the T wave negativity in the three standard leads in

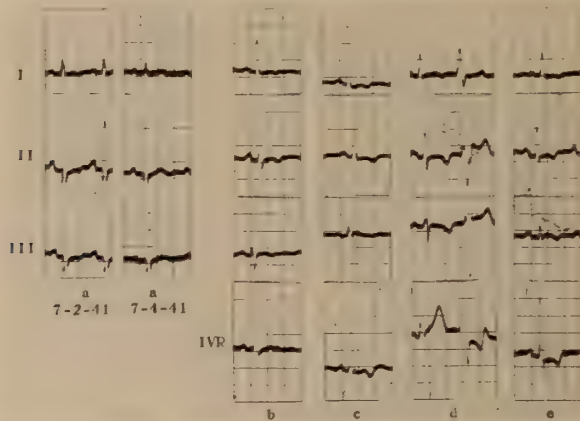


FIG. 4. Electrocardiograms showing negative T waves in the three standard leads obtained from patients who had normal cardiac function.

a. A man thirty-two years of age whose electrocardiographic "abnormality" was discovered accidentally. The heart was normal in size and he led an active life. Electrocardiograms taken two days later were normal.

b. A woman of forty-six years who complained of pain in the left wall of the chest since falling and hitting this region one year previously. No clinical evidence for heart disease could be found and the electrocardiogram showed T wave variations at times approximating the usual normal.

c. A woman thirty-one years of age whose condition was diagnosed as chronic nervous exhaustion and cardiac neurosis. No evidence could be discovered to indicate organic heart disease.

d. A man of thirty-four years whose condition was diagnosed as anxiety hysteria and pharyngeal neurosis. No evidence of cardiac disease was found. Frequent extrasystoles were present at each examination over a period of nine months.

e. A man thirty-five years of age whose condition was diagnosed as cardiac and respiratory neurosis. Some of the symptoms of the effort syndrome were present. The patient had been in an accident when eleven years of age and about a dozen lead shot were seen in the region of the left wall of the chest and pericardium. The possibility exists that the electrocardiogram was representative of an old epicardial injury.

chronic constrictive pericarditis has been emphasized. Examples of the electrocardiographic patterns of pericarditis may be seen in the texts of Ashman and Hull (page 268) and Graybiel and White (3) (page 149) and in the review by Noth and one of us (Barnes). This is one condition in which the chest leads are likely to be negative, usually in all positions across the chest.

Of thirty-eight cases having especially deep inversion of the T waves in

each of the three leads, sixteen had bundle branch conduction disturbances, seven cases had aortic stenosis, another had syphilitic aortic insufficiency and the remainder had hypertensive or coronary disease or a combination of these two conditions. We have noted thirty-two instances in which T_1 was much more markedly negative than T_3 and this has been associated with upright QRS deflections in all three leads as well as with left axis deviation. In twenty-one of the thirty-two cases the diagnosis was severe essential hypertension, in four aortic valvular disease and in the others a combination of diseases including coronary sclerosis. Seventeen cases have been observed in which T_3 was much more markedly negative than T_1 and this, curiously enough, has occurred with roughly the same groups of clinical diagnoses but in only two instances with left axis deviation of the QRS complex.

In eighty-two cases, chest leads were available for study and the T wave of the apical lead was negative in fifty-three, diphasic in nine and positive in twenty cases. In thirty-five cases with the QRS upright in all three standard leads, the T wave in the chest lead was negative in twenty-three, diphasic in four and positive in eight, while in twenty-four instances of well-marked left axis deviation the T wave in the chest lead was negative in seventeen, diphasic in two and positive in five. Where the T wave in the apical lead (usually IV-R) was negative, the T wave in lead I was considerably more negative than in lead III in twenty-six instances and less negative in ten instances. Where the T wave in the apical lead was positive, the T wave in the first lead was considerably more negative than in lead III in four instances and less negative in eight instances.

In only sixteen cases do we have necropsy records and these are mainly from the group of patients having had hypertension and symptoms of coronary sclerosis. The usual findings on post-mortem examination were hypertrophied hearts, severe coronary sclerosis and chronic or patchy infarction of the myocardium. One clinical diagnosis of recurrent pulmonary embolism (fig. 3c) was confirmed at necropsy. In another case of aortic stenosis with hypertension necropsy was performed and minimal coronary disease found. In one case a woman of twenty-three years who had had malignant hypertension and had died of a stroke was examined at necropsy. The heart weighed 630 gm. and there was slight sclerosis of the coronary vessels but histologically no infarction or fibrosis of the myocardium. In one instance in which the electrocardiogram showed a Q_3 pattern, necropsy disclosed an old healed infarct in the posterior basal and septal part of the left ventricle.

COMMENT AND SUMMARY

Inversion of the T waves in the three standard leads of the electrocardiogram, while rather infrequent, has been found to occur in a very large group of conditions which have few correlating factors. With upright QRS

complexes in all three leads (or normal axis deviation) it is not a rare electrocardiographic pattern in aortic valvular disease, particularly aortic stenosis, and in severe essential hypertension in young persons. The same type of T wave inversion in all three leads with left axis deviation has occurred in young persons who had severe hypertension but has not been seen with aortic valvular disease in the same age group. The T wave inversions of this type have also been noted particularly by Kaplan and Katz. They have published electrocardiograms similar to those which we have observed and have emphasized the practical importance of recognizing this concordant type of electrocardiogram in strain of the left ventricle. It may be noted that they did not find it possible to correlate the size of the heart and the type of electrocardiographic pattern, a fact which is in agreement with our teaching over some years. Pardee has published electrocardiograms of the same type without, however, analysis of the condition (page 146 of text). These T wave changes, we believe, may be independent of any concomitantly existing coronary sclerosis, even as the T wave inversion in lead I in hypertension or aortic valvular disease has been proved to be independent of disease of the coronary arteries. We have been unable to find any definite correlation between the size of the heart as seen on the six-foot roentgenogram and electrocardiographic abnormalities under consideration in this discussion.

In regard to coronary disease, we have noted T wave inversion in all three leads as an electrocardiographic abnormality in association with what would appear to be an excellent Q_3 pattern, but only in one instance did it occur with a suggestive Q_1 pattern. We have noted negative T waves in all three derivations after an acute occlusion without characteristic Q changes, as had been noted by Willius and one of us (Barnes), Wilson, Pardee and Weinberg and Katz. The shape of the T waves in these cases with a sharp shoulder following an isoelectric period is particularly important, as pointed out by Pardee. The cases of negative T waves in all three leads associated with right axis deviation are interesting, as the majority have occurred in cases in which there had been recent coronary occlusion. Such a development of right axis deviation following coronary occlusion has been described by Klainer. In a number of instances of severe coronary sclerosis as manifested by increasingly severe effort pain and heart failure, negative T waves have developed in all three leads and necropsy has confirmed the extensive coronary disease and demonstrated generalized patchy infarction without any acute occlusion or large localized infarct. We have noted that after a second coronary occlusion the electrocardiographic relic of the first occlusion may influence the series of electrocardiograms in such a way as to produce T wave negativity in all three leads. While in some instances it is possible that associated pericarditis may play a role in the picture, the early development of the T wave negativity and its orderly retrogression indicate that probably it is all a part

of the infarct pattern. At the present time, we are thus in agreement with Langendorf that a concordant T wave inversion in the limb leads following coronary occlusion is usually to be related to extensive myocardial infarction but that further anatomic correlation studies are necessary. An example of this type of electrocardiogram may be seen in the illustration on page 130 of Ashman and Hull's text.

The study is confusing in regard to an analysis of the effect of digitalis, as there were often no tracings before or after the administration of digitalis. We have noted previously, as pointed out by Herles, that when digitalis was given to a patient showing left axis deviation the greatest effect of medication might be observed in lead I, and conversely in cases of right axis deviation the greatest effect might be seen in leads II and III. It is interesting that in thirty cases in which there was either hypertension or aortic stenosis, in which the patient was receiving average maintenance doses of digitalis and in which the electrocardiogram showed T wave inversion in all three leads, the effect of digitalis in depressing the ST segment had no constant predilection for lead I but often occurred in all three leads and in some instances mainly in lead III. The type of material does not justify further comment at this time. That T wave inversion in all three leads may occur from digitalis is well known and is illustrated in figure 3 and may be seen also in the work of Pardee (page 298) and in that of Graybiel and White (2) (page 152).

CONCLUSIONS

1. A study of T wave negativity in all three leads of the electrocardiogram shows that this abnormality may occur in many conditions.
2. T wave negativity in all three standard leads associated with upright QRS complexes is an occasional electrocardiographic pattern of strain of the left ventricle.
3. T wave negativity in all three standard leads may be an electrocardiographic pattern following acute coronary occlusion and if it is associated with a Q pattern the latter probably will be of the Q_3 type.
4. The behavior of the T wave in the chest leads is not predictable when all three standard leads have negative T waves.
5. A number of cases have been encountered with the electrocardiographic abnormality of negative T waves in all three leads, and in which the heart has been believed to be structurally normal.

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PAROXYSMAL TACHYCARDIA IN VERY EARLY INFANCY

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In 1926 I asked Dr. B. S. Oppenheimer to see a very unusual case with me. It was a three-week-old infant whose pulse was so rapid that it could not be counted even by auscultation over the cardiac area. The child was seen by several experienced physicians, none of whom had previously observed a similar condition. Electrocardiography proved the tachycardia to be due to auricular flutter. The child recovered. Since that time two similar cases have come under my observation. These three cases are worthy of consideration not only because of the rarity of their occurrence but also because of the interesting and unusual clinical picture they present. It seems appropriate to report them in this volume dedicated to Dr. Oppenheimer in view of the important work which he has contributed toward the better understanding of the cardiac pacemaker.

CASE REPORTS

Case 1. History. Patricia J. was born September 28, 1926. She was the second child of healthy parents. The older child was well. Birth weight was 7 pounds 2 ounces. The labor was a normal one and the infant progressed well at the obstetric hospital. She was breast fed. On October 20, when she was about three weeks of age it was noted that her color was somewhat pale, that she refused to nurse, and that she appeared to have periods when, as the nurse described it, "she held her breath".

Examination. On October 22 I was first asked to see the infant. She did not appear to be very ill, although her color was somewhat dusky. The cry was lusty. Her weight was 7 pounds 14 ounces. The most striking features on looking at the infant were her rapid breathing, her poor color and her distended abdomen. On palpation this distention was found to be due to a greatly enlarged liver which could be felt at the level of the crest of the ilium. On auscultating the chest the lungs appeared normal, but the heart was beating so rapidly that its rate could not be determined. There were no murmurs. The heart appeared somewhat enlarged. The pulse at the wrist could not be counted. The remainder of the examination was negative.

It was, of course, evident that we were dealing with some form of tachycardia and an electrocardiogram was taken that same evening (fig. 1). The tracing showed a tachycardia, rate 300 beats per minute. "To each auricular beat there is a ventricular contraction, that is, a 1:1 response. The origin of the tachycardia is definitely supraventricular, probably an auricular flutter, but possibly a paroxysmal auricular tachycardia."

Course. Careful observation by the nurse showed that the tachycardia was not continuous but that there were periods when the pulse would quite suddenly drop to about 150 beats per minute. The infant's condition remained unchanged for 24 hours in spite of sedatives. On the night of October 23 the condition became definitely worse. There was more evidence of cardiac failure, the respirations became very

labored, the lips and extremities became cyanosed and râles appeared in the chest. It seemed as if the infant would not survive. It was then decided to use digitalis, and three minims of Digalen were given hypodermatically. Even this one dose seemed to improve the condition so that it was prescribed regularly thereafter by mouth.

For the next three days paroxysms of tachycardia appeared and disappeared, but the signs of cardiac failure gradually diminished and after the fourth day the infant appeared well. The liver receded and the baby went on to complete recovery.

Due to the fact that the mother (who it should be remembered was nursing her baby) smoked cigarettes to great excess, it was thought that the rapid heart rate of the infant might be due to nicotine poisoning through the breast milk. Nursing was stopped and the breast milk was examined for nicotine by Dr. Robert A. Hatcher of Cornell University Medical College. However, the withdrawal of the breast milk seemed to have no effect and no trace of nicotine could be detected in the milk.

The tachycardia lasted for about four days and then completely disappeared. The patient has been under my observation ever since this episode and has been a very healthy individual. In early childhood she had a severe attack of pertussis, but

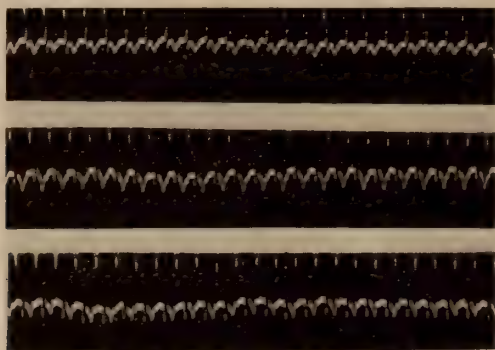


FIG. 1. Supraventricular tachycardia, rate 300 beats per minute
Probably auricular flutter with 1:1 response

no trace of any cardiac signs or symptoms made their appearance. She is at present sixteen years of age and is in excellent health.

Case 2. History. (Adm. 347996). Mortimer G. was the second of two children. The other sibling is living and well. Family history was negative. He was born in a hospital December 19, 1932. Full term, spontaneous delivery and easy labor. No cyanosis or convulsions. Birth weight 6 pounds 10 ounces. Breast fed every 3 hours. Gaining in weight. Weight on admission, (January 16, 1933) at age of four weeks, was 7 pounds 8 ounces. For the first three weeks of life the baby nursed well and seemed perfectly healthy. However, during the week preceding admission the mother noted that the baby became pale and cyanotic while taking water from a bottle. Immediately after feeding the infant's breathing would become shallow. He reacted very differently to breast feeding. Whereas previously he had taken the breast very eagerly, he now had to be forced to feed at all. There was no history of trauma, no twitching or convulsions. There was no vomiting and the stools were good.

Examination. The following positive findings were present: an ashy gray cyanosis of the face, lips and finger tips. Respirations were rapid and gasping. The pulse was imperceptible. The heart rate was extremely rapid, so that the beats could only

be counted approximately (rate 360 (?)). The apex beat was felt diffusely in the third and fourth interspaces just beyond the nipple line. The left cardiac border percussed $1\frac{1}{2}$ cm. to the left of the nipple line; the right border was at the right sternal margin. Sounds were of fair quality. There were no murmurs. The rate was very rapid and the rhythm was regular. The lungs showed no abnormalities. The liver edge was felt 4 cm. below the costal margin. The spleen could not be felt.

Laboratory data. Hemoglobin, 86 per cent; red blood cells, 4,800,000; white blood cells, 18,300; polymorphonuclear neutrophils, 25 per cent; lymphocytes, 34 per cent; monocytes, 5 per cent; metamyelocytes, 4 per cent; myelocytes, 2 per cent. Blood calcium was 10.5 mg. per cent, and phosphorus 3.6 mg. per cent. Except for a trace of albumin, the urine was normal. The temperature was subnormal. An electrocardiogram taken on admission showed auricular flutter with a 1:1 ratio and a rate of 310. Numerous subsequent electrocardiograms revealed auricular flutter (fig. 2). Two of them taken immediately after calcium gluconate injection showed sinus rhythm with rates of about 160 to 170.

A roentgenogram of the chest taken January 21 was reported as follows: "Examination of the chest shows a shadow in the right cardiophrenic angle which has the

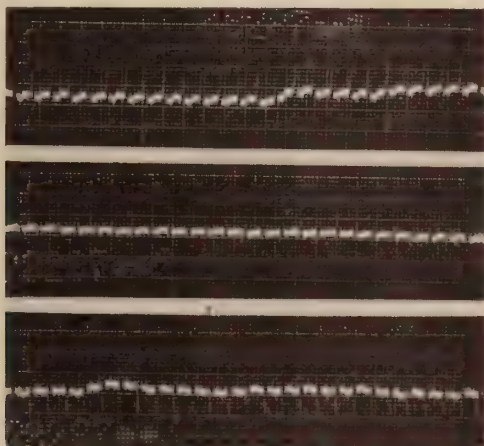


FIG. 2. Auricular flutter with 1:1 response. Rate 310 beats per minute

appearance of an infiltration. There is an area which is suggestive of pneumothorax in the peripheral part of the right chest. There is a suggestion of widening of the cardiac shadow on the left side. This is less apparent on fluoroscopic examination. It cannot be definitely stated that there is enlargement present."

Course. During the nine days that the child was in the hospital the pulse was very rapid most of the time. The temperature, subnormal on admission, remained normal with the exception of the second, fourth and fifth days when it rose to 102.5°F . Calcium gluconate was given intravenously a number of times with a resulting return of sinus rhythm and a rate of 160 which persisted for two hours, but the tachycardia kept recurring. From the third day on the baby was given digitalis. At times the child seemed to improve, but on the ninth day he suddenly became very cyanotic and died (January 25, 1933).

Necropsy findings. There was hypertrophy and dilatation of the right ventricle, hydrothorax of the right chest (500 cc.); hydropericardium and congestion of the viscera. The heart valves were normal and there were no congenital malformations. Unfortunately the heart was put in an improper fixing solution which destroyed the tissues so that microscopic study was impossible.

Case 3. History (Adm. 395311). On July 1, 1936 I was asked to see baby Carol M. who had been hurriedly sent to The Mount Sinai Hospital with the following history: She was aged four months and was the first child of healthy parents and had been in excellent health up to three days before admission. The first indication that there was anything wrong with the infant was on June 29 when she vomited several times. The following day she was seen by her pediatrician. Her temperature was 100.5°F., respirations 40 per minute. Except for harsh breathing over both lungs, no abnormalities were noted. The baby's pulse rate was not observed. That evening the temperature rose to 102°F.

On July 1 at 10 A.M., when again seen by the physician, the physical findings were unchanged. The color was good, the respirations were still 40 per minute. The abdomen was carefully palpated and appeared normal. The physician told the

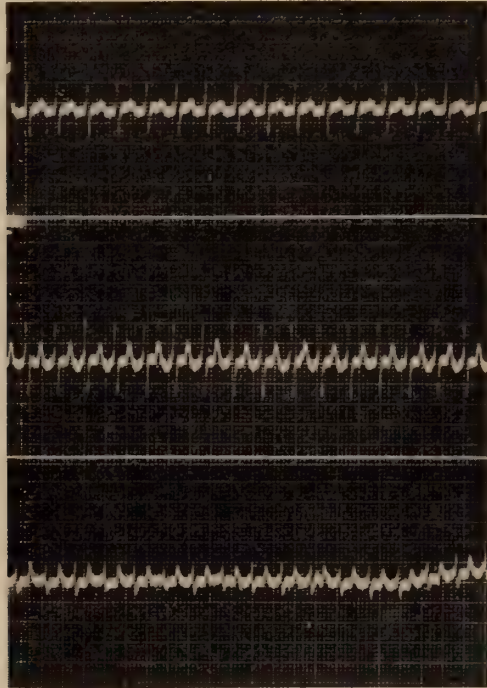


FIG. 3. Auricular tachycardia rate 210 beats per minute. P (auricular) waves are large

mother he believed the condition to be a mild infection of the upper respiratory tract. At 1 P.M. the mother noticed that the child's hands and feet became very cold. Fifteen minutes later the baby became very cyanotic and was rushed to the hospital.

Examination. When seen at 4 P.M. the infant appeared *in extremis*. The salient features of the physical examination were as follows: The lips and extremities were deeply cyanosed. The respirations were extremely rapid and noisy. The pulse could not be felt. The skin was cold and clammy. The temperature was normal. Loud coarse râles were present over both chests and the respirations were so noisy that proper auscultatory examination was impossible. The heart sounds were not audible due to the noisy type of respiration. The abdomen was somewhat distended and the liver edge was felt about at the level of the umbilicus.

Course. These findings, especially the enlarged liver, suggested cardiac failure rather than pulmonary infection. Of particular importance were the absence of

fever and the great enlargement of the liver which the physician assured me had not been present six hours previously. Paroxysmal tachycardia was suspected and an electrocardiogram and roentgenogram ordered. Stimulants, digitalis and oxygen were administered, but in spite of treatment the infant expired late that afternoon.

The roentgenogram was reported as follows: "Examination of the chest shows no definite abnormality of the lungs. However, since the examination was made at the bedside and there is considerable exaggeration in the size of the heart, it is probable that a process might be obscured on the left side."

The electrocardiogram was reported as showing "supra-ventricular paroxysmal tachycardia, rate 210, probably arising in the auricle" (fig. 3).

DISCUSSION

These three cases resemble each other in that they are all examples of extreme tachycardia occurring in very early infancy. In two of the infants the condition was first noted at the age of three weeks, in the third at the age of four months. One infant recovered, two died.

Under the title of paroxysmal tachycardia or auricular flutter, cases of this kind have appeared in the literature from time to time since the first case was reported by Werley in 1925. The latest and most complete article on the subject is by John P. Hubbard, who reports nine cases of paroxysmal tachycardia in infants under one year of age. The fact that six of these nine cases were encountered during one year prompts this author to suggest that these "cases may occur more often in the early months of life than has heretofore been recognized." From the literature he was able to collect only nineteen proven cases. At The Mount Sinai Hospital only two cases have been recorded which are included in the three reported here. It is true that there is no obstetric service at this hospital and that, therefore, the number of newborn infants is limited, yet if the condition were not uncommon one would expect at least an occasional case to have been admitted.

Apparently if paroxysmal tachycardia attacks the infant during its first year it is more likely to be during the first few weeks of life, for of the thirty-one cases of which we now have records, twenty-two were aged one month or less at the onset of the disease. No known cause for this syndrome has been discovered and the condition in many of the cases is first noted when symptoms of congestive failure make their appearance. Occasionally the rapid pulse is accidentally discovered in an apparently healthy infant as in one of Hubbard's cases, in which the tachycardia was found on a routine examination for discharge from the obstetric hospital. I was asked to see all three cases here reported because there had been evidence that the babies were ill. All of the patients had vomited. In all there was a pallor and refusal to take food. In all a very striking feature was a marked enlargement of the liver. In fact the diagnosis in Case 3 suggested itself because of the rapid development of hepatomegaly. It may be noted that in this case a physician had carefully examined the abdomen at the onset of the illness and had failed to find enlargement of the liver. Twenty-four hours later, when I first saw the infant, the liver was found to have

reached almost down to the crest of the ilium. Since the noisy respirations, due to pulmonary edema, completely obscured the cardiac sounds and since the pulse could not be palpated, severe cardiac failure was diagnosed. In the absence of fever and in the absence of history of a previous illness, sudden congestive failure in a young infant is extremely rare. An electrocardiogram was ordered because of the possibility that paroxysmal tachycardia might be present. It is, therefore, important to keep in mind the fact that congestive failure in a young infant may be due to this disturbance of cardiac rate.

In both Case 1 and Case 2 the tachycardia responded to medication. Case 1 was definitely saved by digitalization. However, even after the drug was administered and the heart rate fell and a sinus rhythm was reestablished, the tachycardia would reassert itself and continue for many hours. Finally, however, after three days the heart rate became normal and remained so.

In Case 2 calcium gluconate injections reduced the rate for several hours, but the flutter always returned. Of interest is the fact that injection of normal saline solution accomplished the same thing, although sinus rhythm continued for but a few minutes. Large doses of digitalis failed to save this infant.

In Case 3 evidence of the disease apparently first appeared at the age of four months and the attack was so violent that death ensued in three days. As no autopsy was obtained in this infant, it is possible that some pre-existing cardiac anomaly may have been present (congenital hypertrophy?).

The article by Hubbard, referred to above, so thoroughly covers the subject of paroxysmal tachycardia in young infants that it seems unnecessary to go into great detail here, and only a brief resume of the salient features of the illness will be presented.

The exact cause of paroxysmal tachycardia in the very young infant is not known. There do, however, seem to be two types of the disease, one in which the cardiac irregularity appears quite spontaneously without any discernible cause and the other in which it is secondary to some definite ascertainable pathology, i.e. rhabdomyoma of the conduction system (Wegman and Egbert), idiopathic cardiac hypertrophy (Powers and LeCompte), meningitis or encephalitis (von Bernuth). Case 1, here presented, clearly belongs to the first group as does in all probability Case 2. In this group one must postulate some neuromuscular disturbance similar to what we see in cardiospasm or pylorospasm. One can conceive a temporary difficulty in the complicated neuromuscular mechanism of the heart beat, a so-called functional disturbance. This immediate disturbance can be remedied by digitalis, after which the heart returns to its normal rhythm and the functional difficulty remains permanently corrected. Neither the type of labor nor the health of the mother during pregnancy appears to have any bearing on the occurrence of tachycardia in the infant. The occurrence of disturbed cardiac rhythm in tetany led us to suspect the possibility

of abnormal calcium metabolism; however, the calcium and phosphorus determinations in my second case resulted in normal findings, and the administration of calcium did not bring about any lasting beneficial results. In my first case nicotine was suspected, but no incriminating evidence could be produced. This group may well be termed "idiopathic" in the sense that the disease is due to a temporary functional disturbance of undiscoverable origin in the cardiac mechanism. The symptomatology is rather characteristic, the most important complaints being cyanosis, vomiting, dyspnea, anorexia, and restlessness. On examination not only is the tachycardia striking but the unexpected finding of great enlargement of the liver is characteristic. The heart rate may be very rapid, a rate of 464 being recorded in one case (Sherman and Schless); as a rule, however, it runs between 250 and 300 beats per minute. The beats are quite regular and the rapid rate may be maintained for many hours at a time. For no known reason the attack may subside for a short time to recur without any ascertainable cause. In adults paroxysmal tachycardia is usually accompanied by some degree of block; the rapid beats arising in a focus in the auricle are not all transmitted to the ventricle so that, for example, the auricle may beat twice as fast as the ventricle. In the young infant, however, the ventricle is able to keep pace with the auricle and we often see flutter with a 1:1 ratio, even when the rate is 250 or more beats per minute, as in Case 1 here recorded.

The treatment of this condition consists chiefly in the administration of digitalis. The 9 cases reported by Hubbard all recovered, 1 without any treatment, the others after receiving digitalis therapy. He recommends 0.05 to 0.1 gm. digifoline as the proper dose, to be given intramuscularly. His cases received up to 0.3 gm. in one day. My first case recovered with this form of therapy. My second case received calcium gluconate for one day and then was given digitalis, but failed to respond. My third case received digitalis as soon as I saw it, but as it was already in extremis, neither this drug, coramine, nor immediate oxygen therapy were of avail. Quinine and quinidine have been used with no particular results. In all my cases pressure on the eye-balls or on the neck over the carotid sinus proved valueless. Hubbard tried mecholyl in one case with a severe reaction necessitating intravenous atropine. It failed to relieve the paroxysm.

The prognosis of the disease appears to be fairly good. Of the 31 proven cases, 7 died and 24 recovered. My third case can be said to have received no treatment, since the condition was recognized too late. Case 2 died in spite of vigorous treatment though the administration of digitalis was delayed two days. Digitalis saved Case 1. It is of considerable interest to note that it has been possible to follow up closely the infant here reported as Case 1. This child has remained perfectly well, has been followed for fifteen years and has had no recurrence of any cardiac symptoms. This is the first case that I can find recorded which has been followed for so long a time.

(Bibliography is published in the reprints)

PERICARDITIS AND SUBACUTE BACTERIAL ENDOCARDITIS

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Probably because of its assumed rarity, the association of pericarditis and subacute bacterial endocarditis has received but scant attention in the literature. Some commendable works on subacute bacterial endocarditis do not even mention it; others refer to it very briefly. Libman (1) was of the opinion that: "In subacute bacterial endocarditis, pericarditis is not part of the clinical picture. It might very well occur as the result of pneumonia or some other complication, or it might represent a mixed infection with rheumatic fever." Ten years later he again said (2), "Acute pericarditis is not found in this disease except when due to intercurrent pneumonia, renal insufficiency, and still more rarely to embolic subpericardial lesions in the myocardium." Horder (3), in his Lumleian Lectures, discussed the entire subject, but made no mention of pericarditis in this disease, although in a previous communication (4) he stated that the presence of pericarditis was a point in favor of rheumatic fever in the differential diagnosis of the two diseases. Sir Thomas Lewis (5), reporting on a special study of the occurrence of subacute bacterial endocarditis with bicuspid aortic valves made no mention of the incidence of pericarditis. But Blumer (6) said, "The pericardium does not as a rule show marked lesions. Obliteration of the pericardial sac is recorded in 3.3 per cent of the autopsies, and an equal percentage shows varying degrees of hydropericardium. Acute or subacute pericarditis was noted in 4.6 per cent of the records." Parkes-Weber (7) in 1913 described a case in which pericarditis with serous effusion was found at autopsy. Vegetations were present on the mitral and aortic valves.

In a total of 2000 consecutive autopsies at The Mount Sinai Hospital (from 1933 to date) there were found 43 cases of subacute bacterial endocarditis, 8 of which (about 16 per cent) showed some form of pericarditis. A review of these eight cases and others mentioned in the literature suggests that each falls into one of the following three groups as regards its etiology and pathology.

1) The pericarditis may be purely "rheumatic"—the rheumatic lesions being old or fresh, and entirely confined to the heart structures or existing as part of a more or less clinically typical case of rheumatic fever. The pericarditis is usually acute or subacute and evidenced by a serous effusion, or the familiar fibrinous shaggy heart. With this may be present an old, inactive process represented by white fibrous patches or a partial obliteration

of the pericardial sac. It may be added that generally the diagnosis is not made during life because unsuspected, unless the case has been under observation during the active rheumatic phase and before the advent of the subacute bacterial endocarditis. Bacteriological studies of the fluid and pericardial tissues are, as usual, negative.

2) The pericarditis may be due to lesions arising from the subacute bacterial endocarditis, any rheumatic elements being absent or definitely old and inactive. In this group the pericarditis is always acute and coupled with an effusion which may become very large. Bacteriologic studies often show the *streptococcus viridans*.

3) In this group the lesions of both the first and second groups may be, and often are, found. Those due to the subacute bacterial endocarditis are responsible for the acute elements in the picture. The severity and extent of the existing rheumatic pericarditis varies considerably, and, if it is an old process with adhesions of an obliterating nature, it will limit the amount and extent of the effusion that may arise subsequent to the development of the lesions of subacute bacterial endocarditis. The presence of this effusion may remain unrecognized and its various manifestations become merged with or confused in the existing clinical picture, particularly if superimposed on an active rheumatic pericarditis with effusion already present.

There are two varieties of pericarditis which do not belong in this discussion, as already noted by Libman: the one due to direct extension from an adjacent pneumonia or pleurisy, with varied bacteriology; the other that seen in the terminal uremia resulting from the glomerular lesions of the "healed" cases.

The pathogenesis of the pericarditis from lesions due to subacute bacterial endocarditis is based on several factors which, in the order of frequency, are as follows:

a) An intimal lesion in a sinus of Valsalva which erodes the wall of the aorta and finally, by extension of the inflammatory process or by actual perforation of the ventricular wall, which is here very thin, reaches the pericardial sac surrounding the base of the aorta through the pericardial wedge. The site of this lesion in the aorta is an area subject to stress and strain during both the systolic and diastolic phases of the heart's action. It is predisposed to trauma and bacterial implantation, favoring dilatation, inflammatory extension and hindering the healing process. This explanation was suggested by Gross and Fried (8). Such a lesion is seen in figure 1.

b) A small subepicardial area of focal myocarditis with extension or rupture into the pericardial sac. Such areas have been shown to result from the occlusion of minor branches of the coronary arteries by bacteria-laden emboli broken from the vegetations. Perry (9) in this connection considered the cellular foci found in the myocardium as almost certainly embolic in origin. de Navasquez (10) was of the same opinion and felt that not only are the obvious vascular lesions embolic (fig. 2) but also the ap-

parently extra-vascular ones, (consisting of foci of leucocytes with or without necrosis of the parenchyma), because so often it was possible to find traces of a more or less necrotic vessel wall in the center of such an area. Furthermore, it can frequently be demonstrated in serial sections that these



FIG. 1. (Case 2.) *A* shows intimal lesion on the edge of a large mycotic aneurysm at base of aorta, the necrosis extending through the aortic wall and pericardial wedge. *B*, pericarditis.

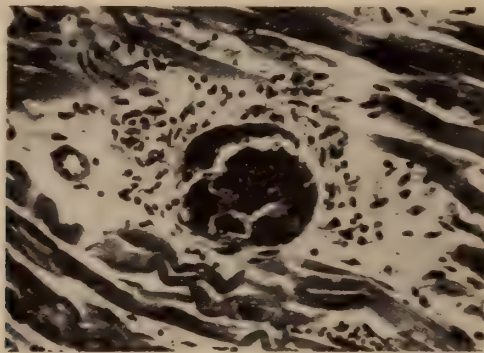


FIG. 2. Myocardial lesion consisting of a fragment of vegetation in an arteriole surrounded by a cellular reaction. Vessel wall is necrotic (After de Navasquez).

areas surround arterioles and capillaries which are visible above and below the level of the lesion (fig. 3). He showed also that the shape, structure and staining properties of the intravascular masses suggest that they are fragments of vegetations embolized into coronary branches with a resulting inflammation or necrosis of the vessel wall. When found, the bacteria in

these occluding masses were shown to be similar to those grown from the vegetations. Bacteria were not demonstrable in all the emboli, though structurally these were recognizable as fragments of vegetations. It is not improbable, he said, that though not evident in sections, bacteria were present originally and then destroyed in the subsequent tissue reaction. As is known, these lesions show a marked tendency to heal. Incidentally, he stated that because of its ambiguity and uncertainty of origin and definition the term Bracht-Wächter body should be dropped.

Saphir (11) in describing the myocardial lesions in 35 cases of subacute bacterial endocarditis also mentioned the tiny infarcts and the perivascular cellular infiltrations. He cited five cases in which bacteria were found in the emboli and one case in which a fragment of vegetation was definitely recognized as an embolus. The small abscesses seen in the myocardium were considered to be the result of bacterial emboli in minute vessels.

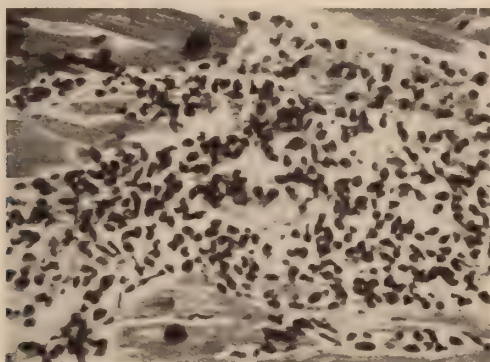


FIG. 3. Myocardium showing a focus of polynuclear infiltration. Although no vessel is visible, studies of serial sections showed the relation of this focus to an embolized vessel (After de Navsquez).

c) Rupture or inflammatory extension through the epicardium of a gross mycotic aneurysm of a coronary artery or one of its larger branches. The results here are obvious.

d) Involvement of a coronary ostium by vegetations and/or the occlusion of a main coronary artery or one of its larger branches by an infected embolus. This initiates a process such as is described under b.

The comparative rarity of rheumatic pericarditis in subacute bacterial endocarditis may divert attention from the real frequency of the latter's association with rheumatic fever in one or another of its manifestations, particularly endocardial and myocardial. Libman in 1913 reported a case in which the heart showed fresh lesions of active rheumatic fever and the typical verrucae of subacute bacterial endocarditis. Leary (12) reported a similar case in 1932. Blumer made the statement that 50 per cent of patients with subacute bacterial endocarditis gave a history of rheumatic fever, chorea, or tonsillitis. Thayer (13) stated that in his series, subacute

bacterial endocarditis had developed on a valve with old rheumatic lesions and that 65 per cent of these patients gave a history of rheumatic fever. White (14) recorded that 4 per cent of patients with rheumatic cardiac disease subsequently die of subacute bacterial endocarditis.

Most frequent and important, however, are the reports of extended histopathological studies showing in a large proportion of cases of subacute bacterial endocarditis the presence of valvular and myocardial lesions characteristic of rheumatic fever. They are found in all stages varying from acute to healed. So frequent is this relationship and so disseminated are these rheumatic lesions that some writers have come to believe that the two conditions—rheumatic fever and subacute bacterial endocarditis—are manifestations of the same disease, differing only in age, severity, etc. Clawson and Bell (16) expressed this point of view. Other observers have even suggested a common bacterial origin for them. Most recent workers, however, disagree entirely with both ideas. They recall the readiness with which a recent rheumatic fever, or one so long quiescent as to be considered healed, will flare up in the course of an intercurrent infection. They indicate only the extremely frequent association of the two conditions and emphasize the implantation of the streptococcus viridans infection on valvular and mural endocardium damaged by the rheumatic fever.

Saphir and Wile (15) reported ten cases of subacute bacterial endocarditis in patients five to nineteen years of age who had been under observation since early childhood. All had a history of a preceding rheumatic infection, and all the hearts showed healed rheumatic lesions. They believe that the two conditions are etiologically unrelated except in so far as a valve damaged by rheumatic fever is predisposed to the development of the other infection on it. Von Glahn and Pappenheimer (17) are of the opinion that the implantation usually takes place onto unhealed, recent rheumatic vegetations. To substantiate their belief in this transition, they found bacteria-free vegetations with the histologic picture characteristic of active rheumatic fever in every one of their series of 26 cases of subacute bacterial endocarditis. In 24 of these the verrucae of subacute bacterial endocarditis and the rheumatic vegetations were on the same valves, as in the cases described by Libman and Leary. In many instances verrucae histologically indistinguishable from rheumatic fever vegetations showed colonies of bacteria in their superficial areas. Gross and Fried, (8b) in 30 out of 42 cases, showed the verrucae of subacute bacterial endocarditis were formed on existing rheumatic lesions.

Worthy of emphasis is the fact that rheumatic fever may be active, as evidenced by fresh lesions particularly noticeable on the valvular endocardium, yet its manifestations may be subclinical, its course unrecognized, and practically chronic. Furthermore, the disease has an interesting and frequent association with subacute bacterial endocarditis.

The eight cases on which this article is based fall roughly into two groups.

The first group of three cases, two men and one woman between the ages of thirty-five and forty-five, had chronic rheumatic cardiovalvular disease on which subacute bacterial endocarditis had developed. At post-mortem examination there was found in each heart an active serofibrinous pericarditis of varying extent, with a moderately increased amount of clear or turbid fluid. In addition, one case showed beginning organization of the epicardial exudate, with adhesions, and another one showed large patches of dense, white, fibrous pericardial thickening, obviously the remains of a previous process. None of the three showed any aortic intimal lesions, penetrating verrucae at the base of the aorta, or any of the small subepicardial lesions which are seen in subacute bacterial endocarditis and which mark the second group of cases. Also, in none of the hearts were there any fresh vegetations which would indicate an active rheumatic fever. Since no other of the usually assignable causes for the pericarditis were found, the assumption is made that it was secondary to an unrecognized rheumatic fever.

The second group comprises the other five cases. (Abstracts of the histories and post-mortem findings are appended.) In these the pericarditis was extensive, with a serous, turbid, hemorrhagic or fibrinous effusion, moderate or large in amount. It was an integral part of the pathology of the subacute bacterial endocarditis. In all of them the aorta or its base was involved and the pericarditis was obviously secondary to a perforating lesion of the aorta or, in one case, of an embolized coronary vessel. The process underlying the subacute bacterial endocarditis varied—in two cases it had developed on a calcareous aortic valve, in one on a congenitally deformed aortic valve, in another on old sclerotic valves, and in the last, on a patent ductus arteriosus.

CASE REPORTS

Case 1. History (Adm. 451937). M. L., a white man, aged 54 years, was in good health until two months before admission to the hospital. He then began to experience transient joint pains, easy fatigue, profuse sweats, and dyspnea on exertion. He lost about twenty pounds in weight and developed low grade fever.

Examination: The chest was emphysematous. The lungs were clear. The heart was enlarged to the left and the sounds were of poor quality. There was a coarse, rough systolic murmur over the entire precordium and a rasping over the aortic area. There was no thrill. The blood pressure was 90 systolic and 60 diastolic. The liver edge and the tip of the spleen were palpable. There was suggestive clubbing of the fingers.

Laboratory data: The blood showed a mild secondary anemia; the sedimentation time was fifteen minutes. The blood chemistry was normal. The blood Wassermann reaction was negative. The urine was clear, acid and had a faint trace of albumin with a few red and white blood cells and a maximum concentration of 1010. Repeated electrocardiograms showed changes indicative of progressive myocardial damage and later of an interventricular block.

Course: During his nine weeks in the hospital various diagnostic procedures, including agglutination tests, were carried out, and found to be negative. The physical findings suggested the possibility of subacute bacterial endocarditis super-

imposed on a calcific aortic stenosis. Eight blood cultures were reported negative and there were no cutaneous embolic phenomena. During the fifth week in the hospital the patient's temperature began to spike, often reaching 104°F. He had severe chills. Precordial pain set in, with a definite widening of the area of cardiac dullness above and the development of a coarse leathery friction rub over the entire precordium. At this time a second x-ray examination of the chest showed a marked increase in the size of the cardiac shadow suggestive of a pericardial effusion. The pericardium was tapped anteriorly and 40 cc. of bloody fluid were readily obtained. This fluid contained innumerable red cells, but no bacteria on smear or culture. Following the pericardial tap the patient appeared more comfortable, having experienced some relief from dyspnea. The blood pressure was now 80 systolic and 60 diastolic; a pulsus paradoxicus appeared. As it seemed possible that a bacterial endocarditis was responsible for the clinical picture, Sulfapyridine was then administered. The patient stood the drug poorly and it was stopped after two weeks. Immediately following the administration of the drug the patient became afebrile for four days, but then the fever returned and persisted throughout the remainder of the clinical course. Because of increasing dyspnea and poor heart sounds, the pericardium was again tapped but no fluid was obtained. The blood pressure was 70 systolic; diastolic pressure was not obtainable. The lungs became moist. It was suggested that shock could explain some of the clinical features. The patient died after nine weeks in the hospital.

Necropsy findings: The heart was markedly enlarged and showed the lesions of subacute bacterial endocarditis superimposed on a calcified aortic stenosis with an acquired bicuspid valve; there was a mycotic aneurysm of the right coronary artery. This had ruptured and led to the formation of a large myocardial hematoma in the wall of the right ventricle, bulging under the epicardium. There was an organizing hemorrhagic pericarditis with obliteration of the entire pericardial cavity; viscera showed chronic passive congestion and there were old infarcts in the spleen and kidneys.

Case 2. History (Adm. 392167). S. L., a white man, aged 53, was first admitted to the hospital in 1936. He gave no history of a previous rheumatic condition. For a year he had experienced increasing dyspnea on exertion. A tooth was extracted six weeks before admission and two weeks later he developed headache, chilliness, fever to 103°F., and night sweats. For one week he was subject to migrating polyarthritides and constant precordial pain.

Examination: The patient was a pale, emaciated, middle aged man. The heart was enlarged to the left; a rough systolic thrill over the base with a loud, rasping systolic bruit over the aortic area and a loud rough systolic murmur at the apex were present. There was moderate peripheral sclerosis. The blood pressure was 90 systolic and 60 diastolic. Sedimentation time was 25 minutes. A blood Wassermann reaction and urine and blood chemistry findings were all negative. X-ray examination of the chest showed a general enlargement of the heart, especially of the left ventricle.

Course: The patient ran a febrile course for four weeks, during which time he was given large doses of salicylates. Various joints became tender and swollen. At one time there was a transient pericardial friction rub. However, fluoroscopy gave no evidence of a pericardial effusion. Circulatory studies were normal. The general condition improved and for two weeks before discharge he was afebrile. No blood cultures were taken at that time. A slight edema of the lower extremities was attributed to hypoproteinemia (3.9 per cent) which had not been modified by two transfusions. He was discharged from the hospital with the diagnosis of recurring acute rheumatic fever (in spite of a negative history); rheumatic cardiovalvular disease—mitral and aortic; fibrinous pericarditis; hypoproteinemia.

The patient was re-admitted about one month later because of joint pains, soreness in both upper abdominal quadrants, and occasional chilliness. There was no evidence of cardiac failure. The heart was enlarged as previously. In addition to the murmur previously found, a faint diastolic murmur was now audible to the left of the sternum. The blood pressure was 90 systolic and 60 diastolic. He ran a moderate fever, and showed conjunctival white centered petechiae. The spleen was not felt; the fingers now suggested early clubbing, and there was a moderate secondary anemia which increased progressively. The urine showed heavy albumin, some red blood cells, and a specific gravity of approximately 1010. The blood protein was 5.6 per cent and later dropped to 4.4 per cent, with normal partition. Chemistry figures were normal. An electrocardiogram showed a P-R interval of 0.3 second. Three blood cultures were negative. The diagnosis of subacute bacterial endocarditis was, nevertheless, maintained. When the temperature became irregular, at times reaching 105°F., it could be brought almost to normal by the administration of 10 grains of Pyramidon given at four hour intervals, and the patient could thereby be made comfortable.

During the course of the illness there was evidence that the patient was developing a focal embolic glomerulonephritis, but there was never a great enough degree of kidney insufficiency to suggest a uremic cause for the pericarditis. There was one episode suggesting a splenic infarction. A blood culture taken shortly before death showed *streptococcus viridans*.

Necropsy findings: The pericardium was dull, thickened and covered with fibrin. The sac contained 100 cc. of bloody fluid. The aortic valve was so distorted that the cusps could not be distinguished and there was marked thickening and calcification. The sinuses of Valsalva were obliterated. There was a slit-like stenosis, aggravated by large, partially calcified vegetations. The ulcerating process had extended from the valve to the base of the aorta, the inner coat of which was destroyed and the rest of the wall dilated to form a large, eroded aneurysmal sac, measuring 4 x 3 x 3 cm. (fig. 1). The base of this cavity was the fibrous tissue of the pericardium. The infection of the pericardial sac had taken place by direct extension through this tissue. Various organs showed evidence of embolization; multiple gross infarcts of the kidney and small hemorrhagic areas which, microscopically, were focal embolic lesions. The pleural cavities contained serosanguinous fluid and the surfaces were covered with fibrinous adhesions.

Comment: No evidence could be found to substantiate the diagnosis of pre-existent rheumatic disease in the heart. No conclusion could be drawn from the appearance of the aortic valve. The mitral valve was thin, delicate, and showed no signs of rheumatic involvement. The chordae tendinae were thin and the insertions normal. The same was true of the tricuspid valve. No MacCallum lesions were present on the auricular endocardium. Sections of the myocardium showed no Aschoff bodies on careful study. However, small embolic areas with inflammatory reaction were seen. The aortic valve may originally have been a bicuspid one, perhaps the seat of arteriosclerotic changes.

As has been noted frequently, the tooth extraction may have served as the precipitating factor in the development of the subacute bacterial endocarditis.

Case 3. History (Adm. 396485). H. W., a white man, aged 24, was well until seven days before admission to the hospital when he developed malaise, fever, constipation and pain in the lower chest anteriorly on deep respiration. The only fact of significance in the past history was that the patient had been told some years before that he had a cardiac murmur. However, he had been able to play college basketball without ill effects. He never had any rheumatic manifestation.

Examination: A well developed, well nourished young man who appeared to be acutely ill. His temperature was elevated, ranging between 101°F. and 104°F.

There were no petechiae. The lungs were negative. The heart was enlarged and the apex was displaced downward; a systolic and diastolic murmur were heard at the apex, and a diastolic murmur at the base and to the left of the sternum. A2 was louder than P2. The pulse was regular. The blood pressure was 125 systolic and 85 diastolic. The liver and spleen were not palpable and there was no clubbing of the fingers.

Laboratory Data: The blood study showed a moderate anemia, and a white blood cell count of 17,000 with 80 per cent polymorphonuclear neutrophils; the sedimentation time was 12 minutes. The venous pressure was 10 cm. The urine was negative except for an occasional red blood cell. The blood urea nitrogen was 14 mg. per cent. The blood Wassermann reaction was negative. Two blood cultures were reported positive for streptococcus viridans, with about 20 colonies per cubic centimeter. X-ray examination of the chest showed marked enlargement of the left ventricle, and a diffuse dilatation of the aorta. An electrocardiogram suggested evidence of acute myocardial or pericardial involvement.

Course: The patient had a stormy course until his death, about four weeks later. He had chills every two or three days; his temperature continued to spike daily, rising at times to 106°F.

The nature of the patient's illness was revealed by the positive blood culture, and the most probable diagnosis was considered to be subacute bacterial endocarditis superimposed on a rheumatic mitral or aortic valve.

Four days after admission he developed a loud scratchy to-and-fro pericardial friction rub at the apex. Shortly thereafter it was noted that the area of cardiac dullness was much larger than on the previous day. X-ray examination confirmed the impression that there had developed a large pericardial effusion. Then signs of fluid appeared at the left base. As the patient's condition was declining rapidly a pericardial paracentesis was performed by a posterior approach. It yielded 200 cc. of slightly turbid straw-colored fluid, specific gravity 1016, with a cell count of 2400, and 66 per cent lymphocytes. The fluid was sterile on culture. The only superficial embolic phenomenon was a bluish, macular eruption on the lateral sole of both feet. At no time was the spleen felt. Shortly before death signs of fluid were noted at both bases. The patient died suddenly, five weeks after the onset of his illness.

Necropsy findings: A moderate amount of clear, serous fluid was found in both pleural cavities. The pericardial sac was greatly enlarged and contained about 500 cc. of serosanguinous fluid. The opposing surfaces of the pericardium were covered by a thick, shaggy layer of fibrino-purulent material and were adherent over part of the base of the left ventricle and right auricle. The left ventricle was considerably dilated and its wall markedly hypertrophied. The right and posterior portions of the aortic valve formed a single cusp, the posterior area of which was markedly thickened and the remainder distorted by large masses of vegetations. These extended into the space between the base of the aorta and the cusp. There was an aneurysmal formation of the base of the aorta extending anteriorly and reaching the epicardial surface at the base of the left ventricle. The left aortic cusp and the anterior mitral valve were involved, but to a lesser extent. Vegetations were also present on parts of the ventricular endomyocardium. The myocardium of the left ventricle for a short distance beneath the aneurysm presented a necrotic, yellowish-brown appearance. The ostium of the left coronary artery appeared free, but the anterior descending branch was lost for a short distance in the necrotic area.

On microscopic examination there were small scattered areas of necrosis and infiltration with polynuclear cells throughout the myocardium. Many of the small vessels showed periarterial round cell infiltration. A culture of the pericardial fluid made at the autopsy showed streptococcus viridans and some post mortem contaminants.

Case 4. History (Adm. 420296). S. N., a white man, aged 65, was well until five weeks before he entered the hospital, when he developed malaise, a productive cough, and fever and was told that he had bronchopneumonia. Since then he had been in bed because of a low grade fever and night sweats. On the day of admission to the hospital his entire right leg suddenly became white, cold, and completely numb, without preliminary pain. He had marked tenderness in the right groin. There had been no previous cardiac symptoms, and no history of syphilis or rheumatic fever.

Examination: The patient looked acutely ill but complained only about his right leg. He had a generalized arteriosclerosis, including the retinal vessels. The percussion outline of the heart was large and the sounds were of poor quality, with a diastolic murmur at the base and a harsh systolic sound at the apex. The spleen was palpable. The condition of the right leg indicated a femoral artery occlusion just below the inguinal fold, with oscillographic readings almost at 0. The blood pressure was 100 systolic and 40 diastolic.

Laboratory Data: The blood findings were not significant except for 2.5 per cent macrophages and a sedimentation time of 30 minutes; the blood Wassermann reaction was negative. The urine contained a faint trace of albumin, an occasional hyaline cast, and a few red blood cells. A blood culture was positive for streptococcus viridans, with 30 colonies per cubic centimeter.

Course: The patient's condition became steadily worse and he died one week after admission.

In view of the man's age and the arteriosclerosis it was striking to note how rapidly a collateral circulation had developed in the affected leg.

The patient, his history negative for syphilis and rheumatism, was believed to have developed subacute bacterial endocarditis on an old arteriosclerotic aortic valve. This was the source of the embolus which lodged in the right femoral artery.

Necropsy findings: The pericardial sac contained a normal amount of clear fluid but there were fresh fibrinous adhesions covering the epicardium around the base of the great vessels. The heart was large and both ventricles were moderately hypertrophied. The mitral valve showed arteriosclerotic thickening and some small flat excrescences on its line of closure. On the endocardium just below the aortic cusps there were large verrucae which extended up over the aortic leaflets, the posterior of which was almost destroyed. There were vegetations in the sinuses of Valsalva with a small aneurysmal dilatation of the posterior sinus extending to the epicardium. The aorta and both coronary arteries showed marked sclerosis as did both common iliaes. An embolus was found in the right external iliac artery. Microscopically there were numerous focal areas of acute myocarditis and myomalacia, and areas of destruction of the intima and underlying tissue at the base of the aorta. Bacteria were present in many of the vegetations.

Case 5. History (Adm. 412490). B. G., a white woman, aged 36, was known to have had a cardiac murmur since her infancy. She was apparently well until nine months before her admission to the hospital, when she experienced the onset of irregular fever, progressive weakness, marked perspiration, and vague generalized pains. One month before admission to the hospital she was treated for pneumonia at another institution. Since that time she had developed marked dyspnea and palpitation.

Examination: The patient was thin and sallow, and had a small petechia in the left conjunctiva and another on the soft palate. There was a small hemorrhage in the right fundus. Dullness, broncho-vesicular breathing and râles were found at both bases. The heart was uniformly enlarged. A loud, rough systolic murmur and a thrill were present over the entire precordium, and a soft diastolic blow was heard at the base. The pulses were equal, regular and Corrigan in type. The blood

pressure was 150 systolic and 20 diastolic, with a pistol-shot and a positive Duroziez sign over the femoral arteries. The liver edge was palpable and somewhat tender, and there were signs of some fluid in the abdomen and a moderate pre-sacral edema.

Laboratory data: The blood studies showed a severe secondary anemia, a sedimentation time of 11 minutes, and a negative Wassermann reaction. Circulation studies suggested some cardiac weakness. Kidney function was normal. X-ray examination of the chest showed considerable enlargement of the heart, particularly of the left auricle, and diffuse congestion of the lungs. The electrocardiogram indicated a left ventricular preponderance and hypertrophy of the auricles. Two blood cultures were reported positive for streptococcus viridans.

Course: The presence of subacute bacterial endocarditis was obvious, but the nature of the cardiac lesion, apparently present since birth and the cause of the loud precordial murmur and the signs of marked aortic insufficiency without cyanosis, was uncertain. The patient gradually lapsed into a terminal stupor seven weeks after admission.

Necropsy findings: The pericardial sac contained 150 cc. of slightly turbid yellow fluid, smears of which did not show bacteria. No pericardial adhesions were found. There were several small hemorrhages in the epicardium and the parietal pericardium near the base. The roots of the great vessels and the auricles were covered with a thin layer of fibrinous exudate. The heart was large and all the chambers dilated and hypertrophied, particularly the right ventricle. Vegetations were attached to the pulmonary valves which showed evidence of chronic inflammation, such as fusion of the commissures. There was dilatation and pocket formation of part of the base of the pulmonary artery just above one of the cusps, and over the base were found several fairly thick, yellowish, irregular intimal plaques. A widely open patent ductus arteriosus was present with both orifices and the intima showing marked arteriosclerotic thickening, and many small vegetations at the pulmonic orifice extending into the lumen, but not reaching the aortic orifice. Other small vegetations were seen over the mitral valve, with changes in the auricular endocardium and the chordae tendinae. The right anterior aortic cusp was perforated and all of the cusps were thickened and covered with large, irregular vegetations; smaller ones were present in the sinuses of Valsalva. Just above the right anterior cusp the wall of the aorta was covered with vegetations which had penetrated the wall but had not entered the pericardial sac.

Microscopic sections showed: extensive necrosis of the media, but little reaction in the adventitia; multiple foci of acute interstitial myocarditis; multiple emboli to various viscera. Culture of the pericardial fluid showed *B. coli*, undoubtedly a contaminant.

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CORONARY ARTERY DISEASE, OBSERVATIONS ON DISPENSARY PATIENTS

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Clinical observations obtained in a dispensary and general hospital do not always parallel those in private practice. The reasons for this disparity are not always clear. That certain infectious diseases or deficiency diseases should appear in greater numbers among those who seek medical attention in general clinics is easily understood. Likewise, the fact that prognosis is frequently unfavorably influenced by conditions of existence of those in the lower income group. But that the same illness should manifest itself differently in the two classes of patients seems hardly credible. Yet it is this possibility which forms the background for the present discussion.

Coronary artery disease in its widest sense has been extensively discussed verbally and orally in recent years. The picture of progressive narrowing of one or more of the ramifications of the coronary arteries starting with the syndrome of angina and culminating in either infarction and/or occlusion is familiar to all clinicians. The symptoms and course of a sudden, fulminating attack of acute coronary obstruction are sufficiently common to need no further elucidation. Silent coronary accidents are supposedly not uncommon but hardly the rule. The point is that the clinical picture of effort pain in these rather typical cases, the electrocardiographic findings and autopsy reports coincide so nicely in the vast majority of instances as to make the picture one of ever increasing clarity. The same train of events is not as commonly noted in heart clinics or general hospital practice. The pathological picture of coronary sclerosis, old and recent infarction, coronary occlusion, and myocardial fibrosis, general or localized, is so frequently reported that clinically these diseases probably exist in larger numbers than usually suspected. That they manifest themselves variously or at least differently seems likewise true.

In a review of the deaths and necropsies among patients treated at the cardiac clinics during the past ten years, it was evident that, although coronary occlusion with one or more infarcted areas was noted and verified fairly frequently, the element of cardiac pain as an outstanding symptom was not as commonly encountered as is frequently reported. In this review only those cases are reported in which one or more infarctions were found at necropsy.

CLINICAL MATERIAL

The present study extends over a ten year period (1931 to 1941). The patients, in most instances, were examined by more than one clinician. The advantage of several consultants' point of view under the system is apparent. In practically every instance the patient's hospital and clinic record is a continuous document. In this analysis only autopsied cases will be utilized. The correlation of clinical histories, electrocardiographic records, course of the illnesses and anatomical findings may be assumed in every instance.

During this period 1944 cardiac patients of every description were under observation. There were 746 deaths and 194 autopsies. The anatomical diagnosis of "coronary heart disease" with resultant myocardial changes was made in 36 instances. The number of times the pathologist was the first to disclose this picture was eight, which would indicate no preagonal evidence of any disturbance in the coronary circulation.

Among the 36 patients examined and autopsied there were 25 whites and 11 negroes. The youngest was 30 and the oldest 76. A few very old patients with obvious general deterioration were excluded. There were 30 males and 6 females. They were mostly hard working people and their habits ranged from the worst to the most exemplary.

CASE REPORTS

Group A. Included in this category are four patients, the only ones with classical case histories of coronary occlusion with substantiating electrocardiographic findings. As an example one such case is transcribed:

History. C. H., a white female, aged 68, was admitted to the cardiac clinic on June 20, 1934 with the complaint of severe anginal pain in the precordium radiating to left arm. This was first noted in August, 1933 but had become progressively severe in the past six months. A clinical diagnosis of coronary heart disease with angina pectoris was made. The patient was under observation in the clinic from June to August, 1934 during which time she continued to complain of pain. On August 30, 1934 she was admitted to the Cincinnati General Hospital complaining of oppressing precordial pain, shortness of breath, with lancinating death-like pain radiating up the left side of the sternum to the left shoulder and down the arm. An electrocardiogram showed evidence of coronary sclerosis. The blood pressure was 135 systolic and 85 diastolic. Death occurred suddenly on September 10, 1934.

Necropsy Findings. Coronary sclerosis with occlusion of left anterior descending branch, acute myocardial infarction, mural thrombosis. . . .

In the entire series there was not a single instance of an acute, devastating, "coronary attack" in a patient well up to that time, nor of attacks of angina pectoris or leg cramps culminating in a final coronary accident.

Group B. In this group, twenty-four in all, pain of any revealing character was conspicuous by its absence. The diagnoses were made by clini-

cal differentiation substantiated by serial electrocardiograms. The patients presented for the most part, either, 1) symptoms of chronic and progressive heart failure (congestive heart failure), or 2) varying grades of disabling dyspnea, frequently only nocturnal dyspnea and unexplained weakness.

CHART I

NAME	AGE	SEX	COLOR	OCCUPATION	PERIOD UNDER OBSERVATION	SEROLOGY
Group A						
D. B.	50	M	W	Gardener	3 months	Positive
M. H.	49	M	W	Orderly	1 year	Negative
L. F.	57	M	W	Not given	2 years	Not taken
C. H.	68	F	W	Baker	3 months	Negative
Group B						
W. W.	61	M	B	Laborer	2 years, 4 mos.	Negative
M. H.	54	F	W	Laundress	4 months	Negative
L. S.	30	M	B	Truck driver	2 years, 4 mos.	Negative
H. N.	73	M	W	Machinist	5 months	Negative
P. W.	32	M	W	Farm work and laborer	10 months	Negative
C. A.	66	M	B	Not given	9 months	Not taken
W. F.	69	M	W	Butcher's helper	1 year, 6 mos.	Negative
J. H.	76	M	B	Laborer	7 months	Negative
W. T.	63	M	W	Painter	5 months	Negative
R. B.	69	M	W	Dresser and packer of chickens	2 years, 9 mos.	Negative
L. G.	52	F	B	Housewife	7 years, 8 mos.	Negative
H. D.	64	M	B	Laborer	2 months	Negative
W. G.	53	M	W	Odd jobs	1 month	Negative
J. T.	62	M	B	Laborer	4 years	Positive
H. B.	61	M	W	Lumber yard worker	1 month	Negative
H. W.	67	M	W	Laborer	5 years	Not taken
H. L.	60	M	W	Varied	6 years	Negative
C. B.	54	M	W	Salesman	2 years, 5 mos.	Negative
J. R.	69	M	W	Watchman	7 years	Not given
J. Z.	70	M	W	None	1 year	Negative
J. W.	46	M	W	Printer	7 months	Positive
H. C.	66	M	W	Foreman	2 years, 4 mos.	Positive
E. S.	68	M	W	Coffee brewer	1 year, 5 mos.	Negative
N. G.	48	F	W	Cook	2 months	Negative

It will be noted in Chart I that there were many more males than females and twice as many whites as negroes. The youngest patient was thirty and the oldest seventy-six years, with the largest number in the fifth and sixth decades. With the exception of a very few, the period during which the patients were under observation was from several months

to two or more years. Yet in this entire time pain referable to the heart was never an important factor. Certainly it was not the complaint which compelled the patient to seek treatment. One case will illustrate the type of patient represented in this group:

History. M. H., a white female, aged 54, a laundress by occupation, requested treatment at the heart clinic on September 25, 1935 because of marked swelling of

CHART II
Group C

NAME	AGE	SEX	COLOR	OCCUPATION	PERIOD UNDER OBSERVATION	CLINICAL DIAGNOSIS	AUTOPSY DIAGNOSIS	E. K. G.
W. P.	49	M	B	Laborer	2 months	Syphilitic heart disease aortic insuff. (Wass. 2 plus)	Coronary occlusion myocardial infarction aortic ins.	Slurring QRS Lead II and III
C. H.	61	M	W	Machinist	8 days	Syphilitic heart disease	Partial occlusion diffuse fibrosis	Intraventricular block
F. S.	34	M	W	Freightman	4 months	Rheumatic possible Ayerza's disease	Multiple infarcts	Left bundle branch block
C. A.	64	M	W	Salesman	1 year, 5 mos.	Arteriosclerotic heart dis.	Recent and old infarcts	Not remarkable
A. B.	49	F	B	Housework	1 year, 8 mos.	Hypertensive heart disease	Multiple scars of old infarcts	Not remarkable
J. S.	49	F	B	Cook	5 months	Malignant hypertension	Myocardial infarct and scars	Not remarkable
W. W.	53	M	B	Laborer	9 months	Hypertensive heart disease	Coronary sclerosis and infarct	Not remarkable
T. W.	73	M	W	Laborer	2 months	Arteriosclerotic heart dis.	Myocardial infarct	Varying grades of block

both legs, and increasing dyspnea of four months' duration. A somewhat milder attack, yielding to rest and treatment, had occurred four years previously. She was found to have a greatly enlarged left heart; the blood pressure was 235 systolic and 140 diastolic; a right hydrothorax and chronic passive congestion of the liver and lungs was present. The vessels of the fundi showed advanced arteriosclerotic changes. The electrocardiogram showed a bundle branch block and left axis devia-

tion. A stormy course of six months during which the patient had a pulmonary infarct ended in death.

Necropsy findings. Multiple recent and old myocardial infarction and organizing mural thrombus, recent and old pulmonary infarction, myocardial hypertrophy. . . .

In this case, as with others in the group, invalidism was due to increasing heart failure extending over a fairly long period, dyspnea, dropsy and weakness being her chief symptoms. Again, pain was not an outstanding feature neither in her past history nor during the course of her illness. The negative results of serological examinations are noteworthy. Likewise the fact that in practically every patient there was marked elevation of blood pressure is noteworthy.

Group C. In this category are a group of eight cases with erroneous diagnoses, but which the pathologist found to be definitely due to coronary occlusion (Chart II). In only one patient was syphilis a factor (W. P.), as substantiated by the microscopic diagnosis. In another patient (C. H.) the history of syphilis was unmistakable, the serology was negative and the pathologist made no mention of the incursion of this disease.

At no time in the supervision of these patients was the probability of coronary disease mentioned nor was there any reason for so doing. The electrocardiograms were certainly not revealing and the patients' histories were not even suggestive of any disturbance in the coronary circulation. The clinical course of each of these patients was that of progressive congestive heart failure.

COMMENT

In this study, those cases showing generalized arteriosclerosis with this lesion noted in varying degrees in the coronary arteries with myocardial fibrosis are not included. Quite naturally there are many such cases. The anatomical diagnosis of infarction was the criterion of selection of cases for scrutiny. There is a vast difference in these two types of heart disease.

In his report of 300 cases of myocardial infarction, Bean (1) observed among other things, that "a prodrominal period of pain occurred in 16 per cent of acute attacks" . . . and again that "Pain and congestive failure occurred together in many cases. Dyspnea was the most frequent symptom and when associated with a sense of constriction merged into the ill-defined domain of pain." One-third of his cases showed signs of congestive failure before acute infarction.

It is a difficult matter to appraise the element of pain in many instances, but it hardly seems probable that with many people acute severe cardiac pain of any appreciable duration could be relegated to the limbo of forgotten miseries. No constant morphological findings have ever been noted to account for the vagaries of pain, its presence or absence, its location or radiation. Some evidence would indicate that it is conditioned by individual differences, a cerebral rather than a cardiac function.

It is important to recognize that a fairly large number of patients suffering myocardial infarction one or more times need not experience appreciable pain. At least their misery incident to devastating dyspnea and the other tragedies of congestive failure may be such as to minimize the element of pain in the picture. Only four individuals of this group of 36 patients had complained of stenocardia. The others conformed to the picture of congestive failure. Dyspnea was the most frequent early symptom and was the one which caused invalidism. Edema of varying magnitude appeared somewhat later but in just as many instances. The arterial blood pressure was found to remain elevated in a very large number of cases, although there was a tendency toward declining levels. The three clinical symptoms, elevated arterial blood pressure, increasing dyspnea and edema certainly overshadowed pain as criteria for the diagnosis of coronary occlusion. The electrocardiographic studies were most revealing as aids in diagnosis. It is doubtful whether many of the diagnoses in this series of cases could have been definitely established without such records. Moreover, the accuracy of determining anterior infarction was noteworthy.

One possible explanation of the absence of those cases of sudden acute attacks of coronary occlusion arises from the fact that most of the patients are emergencies and are immediately hospitalized and among whom the immediate fatality rate is quite high. The number is not great, and compared to the experience in private practice the clinical events show considerable differences. Coronary artery sclerosis may exist sub-clinically for many years and the care a patient can be accorded is of considerable importance to his comfort and longevity.

CONCLUSIONS

1. Thirty-six (18 per cent) cases coming to necropsy (1931 to 1941) were found to have myocardial infarction and coronary occlusion.
2. Only four (11 per cent) patients had ever had actual attacks of "cardiac pain."
3. Dyspnea, congestive failure and elevated arterial blood pressure were the outstanding symptoms.
4. The importance of recognizing the picture of coronary obstruction with infarction, as associated with congestive failure only, and not necessarily pain, is stressed.

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LIGATION OF THE SPLENIC ARTERY FOR THROMBOCYTOPENIC PURPURA AND CONGESTIVE SPLENOMEGALY

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The ligation of the splenic artery is considered a more conservative type of surgical procedure than splenectomy. Because of the simplicity of the operation, it has appealed to some of the clinicians and surgeons of Europe. Its evaluation is based, however, on a small number of cases in comparison to the larger number of splenectomies reported. This led the authors to study the problem and to resort to this procedure in six cases; viz., in two cases of thrombocytopenic purpura, three cases of cirrhosis of the liver with splenomegaly, and fascial constriction (18) of the artery (Payr's operation), in one case of osteosclerotic anemia (myelofibrosis), or non-leukemic myelosis.

Before presenting the case histories and results of the operation, it is well to give a brief review of the literature and previous results of ligation of the splenic artery in both animals and man.

Experimental ligation of the splenic artery in animals. The chief object in ligating the splenic artery in animals was two-fold; to investigate the possible reduction of the size of the spleen or induce its atrophy, and to diminish its hypothetical function. The first experiments of this type were carried out by Heusinger (10), in 1817, who observed that ligation of the main arterial branches of the spleen did not bring about a necrosis. Later, Carrière and Vanverts (5) continued these investigations. They ligated the pedicle of the spleen and succeeded in obtaining a necrosis of the organ, whereas ligation of the artery alone was followed by atrophy of the spleen.

Further investigations have since been made by Storti (20) on dogs, cats, rabbits and guinea pigs. After ligating the splenic artery, he paid special attention to the hematological changes. His deductions were as follows: Ligation of the splenic artery was never followed by any shock or untoward complications; there was no evidence of necrosis; ligation of the splenic artery induces a sclerosis of that organ with loss of power of contractility; blood changes followed ligation, simulating that of splenectomy; and that there is a diminution of the hemolytic factors which last a long time after such intervention.

It is to be kept in mind, however, that in normal animals with a normal

sized spleen it is possible to induce atrophy of the organ by ligation of its artery and thereby eliminate or reduce to a minimum its functions of hemolysis, thrombocytolysis and reservoir.

Ligation of the splenic artery in human subjects. The first attempts to shrink the spleen consisted of multiple ligations of both veins and arteries at the hilum of the spleen. This procedure was followed by Kuester (11), in 1882, in a case of leukemia, by Wells (27), in 1889, for an unusual cystic disease of the spleen, by Wyman (28), in 1889, in a case of malaria with a large spleen, and by Battle (2), in 1893, in a case of rupture of the spleen. An immediate favorable result was obtained by Wells, but in one case this procedure was followed by necrosis of the spleen. A fatal outcome resulted in the others.

The first ligation of the main trunk of the splenic artery in a human subject was performed by Lanz (12), in 1914, on a woman twenty-four years of age who presented a large ectopic spleen. Six months later, another operation was performed and the spleen was found to be completely shrunken. Blain (3), in 1918, reported the first case of ligation of the splenic artery in Banti's disease. Splenectomy was virtually impossible as the spleen was bound down by extensive adhesions. The main vessel was located about three centimeters from the hilum. The spleen shrank to virtually one-fourth its size immediately following the operation. At the end of three weeks an abscess formed at the site of the operation and pointed in the wound. This was incised and found to contain necrotic splenic material. A similar case was reported by Cejudo (6). In his patient a similar abscess developed at the site of the wound, which was drained forty days after operation. Considerable splenic tissue was evacuated. After a long convalescence, the patient recovered.

The splenic artery and its variations. The splenic artery is adequately described by Henschen (9). It is the largest branch of the coeliac axis and passes along the upper border of the pancreas, in a tortuous manner, to the spleen where it breaks up into numerous branches which enter the hilum and supply the organ. The branches of the splenic artery are as follows: The *smaller pancreatic branches* which originate from the splenic artery at varying intervals as the vessel courses along the upper margin of the pancreas. They enter and supply the organ; the *larger pancreatic branch* which usually arises from the splenic about the junction of its middle with its left third and enters the pancreas obliquely; the *left gastro-epiploic* which arises from the splenic artery and anastomoses with the right gastro-epiploic; the *vasa brevia* which arises from the splenic artery near its terminal portion and anastomoses with the gastric and left gastro-epiploic arteries; and the *terminal branches*, five to eight in number, given off from the splenic artery.

It may be pointed out that the splenic artery is not uniform in its relation to the pancreas and its distribution, in fact, there is no uniformity

in the splenic artery itself and it may be quite variable. It is important that these variations should be borne in mind by the surgeon. According to Volkmann (25), it may be found in the following locations: behind, or at the tail end of the pancreas (forty per cent); between the pancreas and the hilum of the spleen (fifty per cent); in the hilum of the spleen (ten per cent). According to Ssosan-Jaroschewitch (19), from the study of a larger amount of material (102 cadavers) two main types of vessels were found: the majestic, or one main branch which occurs near the hilum of the spleen, or the split type, where the branching of the vessel occurs far from the hilum behind the pancreas. In rare instances the main branch of the artery may be imbedded in the pancreas.

The splenic artery can be approached either through the gastro-colic ligament, or through the gastro-hepatic omentum. The former route is preferred by Von Stubenrauch (21), while the latter is preferred by Van Goidsenhoven (24). The artery may also be reached through the transverse mesocolon.

Collateral circulation of the spleen. Ligation, or constriction of the splenic artery may lead to considerable atrophy and rarely to necrosis of the spleen. Absence of necrosis is due to the adequate collateral circulation of the spleen. Melnikoff (17) points out that this is due to the two main arterial circuits; namely, the pancreatico-lineal, and the gastro-lineal circulation. Ssosan-Jaroschewitch (19) states that in thirty-one per cent of his cases he found collateral circulation consisting of four main arterial connections; an anastomosis between accessory gastric vessels and the gastric brevia; the pancreatico-duodenal superior and inferior with arteria caudia pancreatica; the arteria-gastro-breves and circulus carona inferior; and the inferior mesenteric arteria and splenic artery. There are also intra-, as well as extra-organic collaterals.

CASE REPORTS¹

I. Ligation of splenic artery for thrombocytopenic purpura

Case 1. Thrombocytopenic purpura. Ligation of the splenic artery. Recurrence of purpura and secondary splenectomy. Fatal relapse one year later.

History (Adm. 372128). M. P., a married woman, 29 years of age. On January 14, 1933, she was admitted to the Medical Service of Dr. George Baehr. She had had frequent nose bleeds and bruised easily for the five years prior to admission. Later, skin hemorrhages followed the slightest trauma. During the month before entry epistaxis became more profuse, the gums began to bleed and assumed a spongy appearance.

¹ Ligation of the splenic artery was performed by one of us (Dr. A. A. B.) in five cases and fascial constriction of the splenic artery in one case. Clinical and hematological observations were made at expedient intervals in the Hematology Clinic of the Out-patient Department (N. R.).

There was also extensive bleeding during the menstrual period. At the same time, marked weakness developed and the skin assumed a pallid appearance.

Examination. She was a well developed young woman. Purpuric lesions were scattered over the upper part of the chest and upper and lower extremities. A soft, blowing systolic murmur was heard at the apex of the heart. The spleen was palpable two fingers below the free border of the ribs.

Laboratory data. Urine was negative. Blood picture, on admission to the hospital, was typical of thrombocytopenic purpura hemorrhagica. It was as follows: Hemoglobin, 48 per cent; red cells, 4,250,000; white cells, 9,400; platelets, 35,000; polymorphonuclear staff, 2.0 per cent; segmented, 36.5 per cent; eosinophiles, 4.5 per cent; basophiles, 1.5 per cent; lymphocytes, 49.0 per cent; monocytes, 6.5 per cent. Coagulation time, 25 minutes; bleeding time, 22 minutes; tourniquet test, positive; clot retraction, none.

Operation. On January 25, 1933 a ligation of the splenic artery was performed under spinal anesthesia. The artery was approached through the gastro-hepatic omentum. The stomach was depressed downward and a somewhat small splenic artery was found behind the upper border of the pancreas. This was ligated. On palpating the vessels at the hilum, pulsation was still felt at the lower part. Another branch of the splenic artery was then isolated at the tail of the pancreas and ligated. A distinct shrinkage of the spleen was then noted. A citrate transfusion of 500 cc. was given after the operation.

Postoperative course. The clinical symptoms remained unchanged for the first five days. The hemorrhagic tendencies subsided for a few days and then there was a recurrence of the bleeding from the nose and gums. A hematoma was found in the wound at the first dressing. The patient improved later and was discharged from the hospital.

Blood picture. Hemoglobin increased from 48 to 62 per cent. On the day of discharge, hemoglobin was 60 per cent, red cells 4,900,000. A marked leucocytosis (30,000 to 50,000) was present six days after operation. The differential count showed a marked increase in neutrophils at first, later a marked lymphocytosis. Coagulation time became normal and the tourniquet test negative. A slight clot retraction developed. Bleeding time remained the same, but was definitely diminished before leaving the hospital. The platelets did not increase in number.

Second admission (July 17, 1933). Since her discharge from the hospital there were episodes of bleeding from the nose, gums and skin. For ten days prior to the second admission, there was a profuse menorrhagia. Since the operation, she noticed a mass in the right groin which caused pain. Three days before admission, it became hard, more painful and attained the size of a small apple.

Examination. There were small petechiae in the right lower conjunctival sac. The gums were oozing and numerous petechial hemorrhagic areas were found on the hard and soft palates. A few purpuric and ecchymotic lesions were present on the lower extremities. The upper abdominal scar was healed. The spleen and liver were not palpable. A large, red indurated swelling was present in the groin. There was no fluctuation.

Laboratory data. The blood picture was as follows: Hemoglobin, 73 per cent; red cells, 3,700,000; white cells, 21,900; platelets, 70,000; polymorphonuclear neutrophils, 65 per cent. Bleeding time, 5 minutes; coagulation time, 13 minutes; clot retraction, present; tourniquet test, strongly positive.

Operation. A splenectomy was performed under gas, oxygen and ether anesthesia. The spleen had considerably diminished in size. One week after operation all tendency to bleeding, including menorrhagia, had subsided. Platelets rose to 80,000. She was discharged twenty-two days after operation, apparently improved.

Follow-up course. After discharge from the hospital she became perfectly well

and remained so, except for an occasional cold. The blood picture showed no evidence of her previous disease.

Third admission (October 14, 1934). Two weeks prior to admission the menstrual flow again became profuse and contained many clots. It lasted nearly seven days, at least two days longer than usual. About ten days previously, she was awakened from a sound sleep by a choking sensation and her mouth was full of blood following a severe epistaxis. Bleeding from the nose continued at the rate of about a drop a second for about six hours despite cold applications. An injection of snake venom was given and the bleeding stopped after two days. There was a recurrence of the purpuric and ecchymotic lesions over the lower extremities, chest and back, which persisted up to the time of admission.

Three days before admission, a gnawing pain developed in the left lower quadrant. On the day prior to admission the abdominal pain became severe and there was extreme weakness. The following day the pain was felt over the entire abdomen. She fainted twice on getting out of bed. A marked pallor of the face appeared at the same time.

Examination. The patient appeared extremely pale and apparently very weak. She constantly complained of faintness. The abdomen was soft and distended. There was a diffuse tenderness in the abdomen, most marked in the para-umbilical region where it was more definite with a slight rebound. The pelvic examination was apparently negative. Although there was no bleeding from the nose or gums, many cutaneous hemorrhages, mostly petechial in size, were scattered over the lower legs, upper extremities and neck.

The impression was that of a recurrence of the thrombocytopenic purpura hemorrhagica with intra-peritoneal bleeding.

A citrate transfusion of 500 cc. was given immediately upon entering the hospital.

Laboratory data. The blood picture was as follows: Hemoglobin, 20 per cent; red cells, 1,420,000; white cells, 17,000; platelets, 70,000; polymorphonuclear neutrophils, 89 per cent; lymphocytes, 5 per cent; monocytes, 4 per cent; myelocytes, 2 per cent. Bleeding time, 5 minutes; clotting time, 4 minutes; clot retraction, present at the end of 45 minutes, but not complete; tourniquet test, positive.

Course. There was marked improvement after two transfusions. Injections of snake venom were given subcutaneously, ascorbic acid 200 mg., intravenously and intramuscularly, daily. She continued to improve until about November 7, when bleeding began again from the nose, gums and vagina.

On November 10 the vaginal bleeding became very profuse, necessitating a transfusion almost daily. It was believed that the bleeding was also retrograde from the tubes or ruptured ovarian follicles. Since some relationship between the ovarian function and the recurrence of the purpura was considered, radiotherapy was advised. Two x-ray applications were given to the anterior pelvis (November 2, 3) without much effect. The abdominal pain began to increase and the abdomen became distended, especially in the suprapubic region. As a final resort, an exploratory laparotomy was performed on November 13, revealing a generalized peritonitis, with foul, reddish, necrotic fluid. Death followed a few hours after the operation.

Comment. This is an unusual case of chronic thrombocytopenic purpura. There was apparently very slight response to ligation of the splenic artery, so that splenectomy was advisable. At the second operation, the spleen was atrophic. Histological examination revealed fibrosis of the spleen, infiltration with numerous eosinophilic leucocytes and many giant cells of reticular origin. The intra-splenic arteries were patent. Following operation, the blood picture returned to normal and the patient was apparently well for one year. The severe menorrhagia and intra-abdominal bleeding recurred and was followed by peritonitis from infection of intraperitoneal blood, and death.

Case 2. Chronic thrombocytopenic purpura. Ligation of splenic artery.

History (Adm. 358312). E. K. D., a married Jewish woman, aged 21. On March 17, 1928, she entered the hospital from the Hematology Clinic with a history that for ten years prior to entry she had had daily nose bleeds, except for a two year interval. For six weeks before admission, she again complained of daily nose bleeds. During this entire period she was never free of ecchymotic lesions.

Examination. The skin was fair and firm in texture. Purpuric and ecchymotic eruptions were scattered over the upper and lower extremities. A rough, prolonged systolic murmur was heard at the apex of the heart. The liver and spleen were not palpable.

Laboratory data. On admission the blood picture was as follows: Hemoglobin, 90 per cent; red blood cells, 5,300,000; white blood cells, 8,800; platelets, 80,000; polymorphonuclear neutrophils, 67.5 per cent; eosinophiles, 3.0 per cent; basophiles, 1.5 per cent; lymphocytes, 21.0 per cent; monocytes, 7.0 per cent. Bleeding time, 9 minutes; coagulation time, 12 minutes; tourniquet test, positive; clot retraction, present but slight. Blood Wassermann reaction, 4 plus.

Course. The blood Wassermann tests were repeatedly positive. Dermatological examination (Dr. H. Goldenberg) failed to reveal any clinical signs of congenital syphilis, except for a suggestion of rhagades around the mouth. A course of treatment with neosalvarsan and bismogenol was given without any apparent effect on the purpuric symptoms or the Wassermann reaction. She was discharged on March 31, 1928.

Second admission (April 24, 1933). After her first discharge from the hospital the purpuric state continued unabated. Several months later, bleeding from the gums recurred and small amounts of blood were noted in the stools. Two weeks before the second admission, her menstrual period was profuse, lasting two weeks, instead of about two days which was the usual period since her marriage in 1932. The tendency to bleed became more pronounced and epistaxis became more profuse and difficult to control. A course of treatment with snake venom was given without any obvious effect.

During this time, periodic intracutaneous venom tests were always strongly positive. From time to time she again received a course of treatment with neosalvarsan and bismogenol, but without any changes in the purpuric condition or Wassermann reaction.

Examination. At this time, there was marked pallor and blood exuded from both nostrils. The heart was enlarged to the right and left, and a loud blowing systolic murmur was heard at the apex. The liver was felt one finger below the ribs. The spleen was not palpable. Numerous ecchymotic lesions were scattered over the lower and upper extremities, and abdomen. Few red blood cells were found in the urine. Again, the blood Wassermann reaction was four plus, but the Kahn reaction was negative.

Laboratory data. The blood picture at this time was as follows: Hemoglobin, 52 per cent; red cells, 3,790,000; white cells, 6,100; platelets, 20,000; polymorphonuclear neutrophils, 73 per cent; lymphocytes, 23 per cent; monocytes, 4 per cent. Bleeding time, 14 minutes; coagulation time, 7 minutes; tourniquet test, strongly positive; clot retraction, slight.

Operation. On April 10, 1933, a typical ligation of the splenic artery through the gastro-hepatic omentum was performed. A citrate transfusion of 500 cc. was given immediately after operation. During the postoperative course of six weeks, her platelets remained at a constant low level, varying from 35,000 to 60,000. The only increase in the blood platelets was noted the day after operation. At that time, they reached their highest level, 100,000 per cubic millimeter. There was consider-

able clinical improvement. There was cessation of the epistaxis, while oozing from the gums continued intermittently, but this at no time was of any great consequence. The patient was discharged on July 1, 1933, and was followed up in the Out-patient Department.

Follow-up course. Since her discharge, she had improved and had a normal menstrual period which lasted about three days. During the latter part of October, 1933, she developed a slight nose bleed which was controlled by packing with ordinary cotton. Three weeks later she noted that she again bruised easily. At this time, spontaneous petechiae began to appear over the lower extremities. Again, there was a feeling of weakness and a loss in weight. Bleeding from the gums later recurred and she complained of buzzing in the ears and faintness. During the early part of November, 1933, the menstrual flow was profuse and lasted five days, during which time she lost a considerable amount of blood. This aggravated her general condition.

Third admission (November 18, 1933). On the day of admission she awoke with a headache, dizziness, extreme weakness, pain in the abdomen and nausea. The abdominal pain was lancinating in character and remained localized about the umbilicus.

Examination. The patient was acutely ill. The gums were spongy and oozing blood. A loud, long systolic murmur was heard over the entire precordium. The blood pressure was 132 systolic and 76 diastolic. Petechiae were scattered almost over the entire body. The liver was barely palpable and the spleen was distinctly palpable at the costal margin.

Laboratory data. The blood count was as follows: Hemoglobin, 34 per cent; red cells, 1,980,000; white cells, 9,600; platelets, 30,000; polymorphonuclear neutrophils, 80 per cent; lymphocytes, 14 per cent; monocytes, 3 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent. Bleeding time, so profuse at the end of 10 minutes that pressure was applied to the ear lobe to stop the bleeding; coagulation time, 10 minutes; tourniquet test, strongly positive; clot retraction, not present.

A few red blood cells were found in the urine.

Course. On admission, a transfusion of 800 cc. of whole blood was given. This was followed by only slight improvement. Splenectomy was contemplated, but about eighteen hours after admission she suddenly became stuporous. The temperature rose to 105°F. There was generalized muscular flaccidity and she became incontinent. She died in a coma twenty-seven hours after the third admission.

Necropsy findings. Subdural hemorrhage of the brain, pulmonary edema, hemorrhagic bronchopneumonia, peri-splenic adhesions, acute infectious splenic tumor, interdentinate endocarditis of mitral valve, hypertrophy and dilatation of left ventricle, parenchymatous degeneration of the viscera, fatty metamorphosis of the liver, persistent thymus. The splenic artery was found to be ligated but no thrombosis distal to the ligatum was present.

Comment. In this case of chronic thrombocytopenic purpura ligation of the main trunk of the splenic artery failed to reduce the size of the spleen and control the symptoms. In spite of immediate shrinkage in the size of the spleen, it was found that five months later the organ was considerably enlarged.

II. Ligation of the splenic artery for congestive splenomegaly (Banti's disease or splenomegalic cirrhosis of the liver)

Case 3. Splenomegalic cirrhosis of the liver.

History (Adm. 359346). P. S., a married woman, aged 30, was admitted to the Medical Service of Dr. B. S. Oppenheimer on April 27, 1931. For three years previously she had complained of excessive eructation, not related to food or time of

eating. Her appetite remained unchanged. There was occasional epigastric rumbling but no other discomfort or pain. During this time she developed an eruption on the face which subsequently subsided with x-ray treatment. At that time her spleen was enlarged, but she was told that her blood was normal.

Eighteen months prior to admission, the patient suddenly developed fullness and discomfort in the abdomen, for which she took some rhubarb and soda. She vomited that night, but was not relieved. The following night she vomited again and noted on this occasion it was bloody. She became very weak and pale and was taken to the Brooklyn Jewish Hospital. She did not vomit while in the hospital, but tarry stools continued for one week. The hemoglobin fell to 40 per cent. She improved and was discharged three weeks later with a diagnosis of Banti's disease. Since her discharge, there was no further hematemesis, but a sensation of abdominal fullness and discomfort at varying intervals. During this time she developed a peculiar sense of stiffness in the upper left quadrant of the abdomen.

Examination. She was an undersized, but moderately well nourished woman with only slight evidence of jaundice. The nasal septum was deviated to the right. The mucous membranes were hyperemic. The heart and lungs were normal. The abdomen was enlarged. The spleen was firm, well defined and descended to the level of the umbilicus. The liver was not palpable.

Laboratory data. The blood picture was as follows: Hemoglobin, 82 per cent; red cells, 4,300,000; white cells, 7,400; platelets, 220,000; polymorphonuclear neutrophils, non-segmented, 13 per cent; segmented, 69 per cent; eosinophiles, 11 per cent; basophiles, 2 per cent; lymphocytes, 14 per cent; monocytes, 1 per cent. Bleeding time, 1 minute; clotting time, 6 minutes; clot retraction, normal; tourniquet test, negative; bromsulphalein test, 35 per cent retention in 33 minutes; stool, negative for blood; icterus index, 30; Van den Bergh, direct, positive, delayed reaction; cholesterol, total 340, ester 158. Wassermann reaction, negative.

Urine showed no albumin, but strong reaction for urobilin.

Course. The patient was readmitted on two subsequent occasions for diarrhea.

Fourth admission (April 17, 1933). The patient was admitted to the Surgical Service of Dr. A. A. Berg. At this time she presented a frank icterus, considerable emaciation and angiomas of the face.

Examination. A harsh systolic murmur was heard over the entire precordium of the heart. The spleen was felt below the umbilicus in the midline and the liver was felt four fingers below the free border of the ribs.

Laboratory data. The blood picture revealed a secondary anemia. The blood platelets were normal. Icterus index was 35, and again the Van den Bergh showed a direct, delayed positive reaction.

Operation. A typical ligation of the splenic artery was performed under spinal anesthesia. The vessel could not be found in the usual location but by palpation its pulsation could be felt in the substance of the middle third of the pancreas. This was incised in order to expose the artery. During the operation, the liver showed a coarse nodular cirrhosis. Immediately following the ligation there was a moderate shrinkage of the spleen.

Postoperative course. About ten days after operation the abdomen became considerably distended as a result of the ascites. The distention could not be reduced by salyrgan. This necessitated tapping at which time eight liters of brownish-yellow turbid fluid were removed. The fluid reaccumulated and ten days later was removed again by paracentesis. In the meantime, the icterus index had fallen to 22. The spleen became distinctly smaller in size and was felt above the umbilicus. On July 1, 1933, she was discharged practically unimproved.

After discharge the condition remained unchanged for about a year during which the ascites did not recur. In December, 1933, she began to lose ground rapidly.

She became very emaciated, the fluid slowly reaccumulated and the abdomen became markedly distended. On the night of December 20, 1933 she lapsed into a coma and died.

Comment. Ligation of the splenic artery in this case of congestive splenomegaly or splenomegalic cirrhosis of the liver reduced the size of the spleen only moderately. The ligation was followed by improvement for one year and the ascites did not recur during this period.

Case 4. Congestive splenomegaly or splenomegalic cirrhosis of the liver; ligation of splenic artery; relapse and secondary splenectomy.

History (Adm. 362280). N. G., a German man, aged 54. On February 25, 1933, he was admitted to the Surgical Service of Dr. A. A. Berg. He was comparatively well until the age of fifty when a severe intestinal hemorrhage developed. Recovery was spontaneous and he remained well for two years when there was a recurrence of repeated gastrointestinal hemorrhages. Following one of these hemorrhages, there was a drop in the hemoglobin to 15 per cent. Repeated transfusions were given and he continued to complain of marked weakness and fatigue on the slightest exertion. Two days prior to admission, a profuse hemorrhage from the stomach developed.

Examination. He was poorly nourished and constantly complained of dyspnea. The heart and lungs were negative. Lymph nodes were enlarged. The spleen was considerably enlarged and could be felt at about the antero-superior spine. The liver was not palpable.

Laboratory data. Blood picture on admission was as follows: Hemoglobin, 17 per cent; red cells, 950,000; white cells, 3,200; platelets, 130,000; non-segmented polymorphonuclear neutrophils, 7 per cent; segmented forms, 71 per cent; lymphocytes, 18 per cent; monocytes, 4 per cent; reticulocytes less than 5 per cent.

Urine examination was negative.

Course. On February 25, 1933, a transfusion of 500 cc. was given, which was followed by an unusually good result. The hemoglobin and red blood cells began to increase slowly.

On March 16, 1933, a second transfusion was given. Following this, the hemoglobin was 31 per cent, red blood cells, 2,400,000, white blood cells, 2,200, and platelets 150,000.

On April 1, 1933, a third transfusion was given. Throughout this period, the white blood cells remained below normal and the platelets fluctuated between 80,000 and 250,000. His general condition continued to be poor and he was considered a poor risk for a major operation.

Operation. April 5, 1933. Before operation, a transfusion of 500 cc. was given. Under gas and oxygen anesthesia and a small quantity of ether, a five-inch left upper rectus muscle splitting incision was made. The spleen was exposed and found to be considerably enlarged. On the surface, a moderate amount of fibrinous exudate was present, indicating the seat of a previous perisplenitis. The liver showed moderately advanced cirrhotic changes. The stomach and duodenum were entirely normal.

An opening was made in the gastro-hepatic ligament, so that the upper border of the pancreas was exposed. A large pencil-sized pulsating, thick-walled splenic artery was revealed. It was then doubly ligated. Following ligation, the spleen was reduced to more than half its size. The opening in the gastro-hepatic omentum was repaired and the abdomen was closed in layers. Following the operation another transfusion of 500 cc. was given.

Postoperative course. The blood changes following operation were as follows: Hemoglobin, 60 per cent; red cells, 4,230,000; white cells, 12,000; platelets, 152,000;

non-segmented polymorphonuclear neutrophils, 33 per cent; segmented forms, 53 per cent; lymphocytes, 8 per cent; monocytes, 4 per cent.

The hemoglobin and red blood cells then gradually diminished until May 11, 1933 when they again began to increase. The blood platelets showed a slight rise within the first few days, 220,000 and gradually diminished to 110,000. By June 30, the hemoglobin had risen to 88 per cent, the red blood cells to 5,200,000, but the white blood cells and platelets resumed their low levels. At this time a slight eosinophilia appeared, but the blood picture remained unchanged otherwise.

The spleen was barely felt at the free border of the ribs.

On May 20, 1933 the patient was discharged after an uneventful convalescence.

Second admission. Patient was free of symptoms until the middle of October, 1933, five months after the operation, when he had another severe hemorrhage from the stomach. A citrate transfusion of 500 cc. was given.

The spleen was felt at about the level of the umbilicus. He continued to have gastric hemorrhages and also passed tarry stools. The hemoglobin usually varied at this time from 12 to 19 per cent, and the red blood cells were about 1,000,000. Leucopenia, as well as a slight thrombocytopenia, persisted. Repeated transfusions were given with little benefit. On November 15, 1933 he left the hospital.

Third admission (February 2, 1934). He re-entered the hospital for further observation. Hematemesis continued and further transfusions were ineffective.

Examination. He appeared very pale. The blood pressure was 100 systolic and 70 diastolic. Ascites was present. The spleen could be felt about three centimeters below the free border of the ribs. The liver was not palpable and could not be percussed. As a last resort, it was decided to perform a splenectomy.

Operation. On February 21, 1934, while a citrate transfusion of 800 cc. was being given, a splenectomy was performed. A left oblique, subcostal incision was made. On opening the abdomen, a large amount of ascitic fluid was evacuated. The spleen was six inches in diameter and was adherent to the stomach, colon and abdominal parietes. The adhesions were very vascular at the lienorenal ligament and there was also a circoid aneurysmal dilatation of the vessels. As the peritoneal portion and lienorenal ligament was divided, some of the vessels were injured and a profuse hemorrhage followed. The vasa brevia between the stomach and spleen were much dilated and numerous. There was no bleeding from the pedicle of the spleen, nor any clots or organized material in the splenic artery or splenic vein. They were clamped before dividing the adhesions so that it is impossible to state whether bleeding would have occurred if clamps had not been applied.

The posterior parietal peritoneum was closed by suture over the splenic stump. A drainage tube was applied to the site of the spleen. The abdominal wall was closed in layers.

The patient lost about ten ounces of blood during the operation. This was readily replaced by the citrate transfusion. He left the operating room in good condition.

Surgical pathology. The specimen revealed an enlarged spleen, weighing 270 gm. and measuring $17 \times 10 \times 3\frac{1}{2}$ cm. The surface was pale grayish pink in color and of a mottled appearance. In general, it was anemic. The splenic notch was accentuated in its lower pole. Its anterior border presented two small yellowish gray hard nodules. These appeared on the surface and protruded on the anterior border. Another nodule, measuring 5 mm. in diameter and calcified in appearance, was present at the hilum. Similar nodules, approximately the same size, could be felt throughout the entire spleen and in its substance; one on the lateral surface and another one on the hilum aspect. The capsule was smooth, except at the anterior margin where it dips into the splenic tissue at about the middle in the form of a whitish gray scar. The splenic artery was smooth and clean throughout. The splenic vein was wide open and the intima was smooth and glistening. There was no evidence of any thrombosis.

On section, the spleen in general appeared anemic; there was a cortical rim which was paler than the remainder of the splenic tissue. As a whole, it appeared fleshy, anemic and was glossy in appearance. The Malpighian bodies were poorly outlined. A calcified nodule, measuring 3 cm. in diameter, was present at one point. The vessels were prominent and revealed no thrombi. Many punctuate hemorrhages, on an average of four to each square centimeter, were scattered over the surface. These were irregular and apparently in relation to the veins as they were situated either around the smaller venules or in close proximity to them. A very small lymph node was present in the hilum of the spleen. This was taken for section.

Microscopic examination. Diffuse fibroadenie of the splenic pulp with conspicuous sinuses and annular hemorrhages. Few fibrosed tubercles.

Postoperative course. There seemed to be a marked improvement the first few days after operation. There was a marked leucocytosis (up to 26,000) with a polynucleosis, mainly of segmented polymorphonuclear leucocytes, with a noted increase in the blood platelets. These continued to rise, so that they numbered 460,000 per cubic millimeter six days after operation. Pneumonia, however, set in two days after operation. He died on February 27, 1934.

Permission for post-mortem examination was not granted.

Comment. The patient remained improved only six months after the ligation of the splenic artery. Symptoms then recurred and in addition ascites. The spleen increased in size after a preliminary diminution so that splenectomy was decided as a last resort. He died after the onset of pneumonia.

Case 5. Congestive splenomegaly or splenomegalic cirrhosis of the liver.

History (Adm. 351604). S. F., an Austrian Jew, aged 37. On May 1, 1933, he was admitted to the Medical Service of Dr. B. S. Oppenheimer. He lived in the United States for ten years after traveling through Africa, Asia, visiting Egypt, Palestine, Syria and other countries. He stated he was absolutely well during this entire period except for diarrhea for three days. Symptoms apparently began eight years prior to admission when he fell off a ledge and struck the left upper abdomen. There was no local injury at that time. Six months later he complained of daily pain in the epigastrium which radiated to the left upper quadrant of the abdomen. He also developed slight drawing pains in both left and right groins.

On entering a clinic, a mass was discovered in the left upper quadrant. He was told this was an enlarged spleen. The symptoms subsided, but he noted the mass was gradually increasing in size. He developed nausea and constipation, for which he took two cathartic pills. This was followed by several black and tarry bowel movements, which had become black and watery. He became weak, somewhat dizzy and began to complain of tinnitus. The next day he vomited a large amount of dark red blood. He again became weak and dizzy.

Examination. The patient was slender, poorly developed, and appeared chronically ill. The conjunctivae were pale and the sclerae were not icteric. The heart and lungs were negative. The abdomen was soft. A firm spleen could be felt two centimeters below the level of the umbilicus. The liver was felt two fingers below the costal margin. Liver dullness was intact.

Laboratory data. The blood count was as follows: Hemoglobin, 58 per cent; red cells, 2,900,000; white cells, 2,200; platelets, 90,000; non-segmented polymorphonuclear neutrophils, 4 per cent; segmented forms, 55 per cent; lymphocytes, 34 per cent; monocytes, 4 per cent; eosinophiles, 2 per cent; basophiles, 2 per cent; reticulocytes, 0.

The blood picture was typical of congestive splenomegaly, Banti's disease or thrombocytopenic splenomegaly, or a possible cirrhosis of the liver with secondary

splenomegaly with blood changes as a result of the splenic enlargement. Thrombosis of the splenic vein and portal vein was also considered.

The patient refused splenectomy, but consented to a ligation of the splenic artery.

Operation. On May 27, 1933, a ligation of the splenic artery was performed, under spinal anesthesia. A left upper rectus muscle splitting incision was made. The spleen was smooth, enlarged and extended to about one inch below the umbilicus. The under surface of the liver was smooth. No free fluid was present in the abdominal cavity. A small incision was made in the lesser omentum and the splenic artery was found coursing through the upper border of the pancreas. It was ligated here at two points, but not divided.

However, during the closure, the patient vomited and most of the sutures were torn. This occurred while the abdominal suture was being passed, so that the spleen was punctured at one point. There was free oozing of blood. A deep suture was taken in the spleen and a piece of omentum tied in over the point of puncture. The abdomen was closed with through-and-through heavy silk sutures.

Postoperative course. Convalescence was uneventful. The spleen was still enlarged, but had shrunk, and was felt above the umbilicus. The blood pictures, however, remained unchanged as far as the leucopenia and blood platelets were concerned. The hemoglobin and red blood cells presented marked improvement. A gradual rise took place, so that by October 29, 1934, the hemoglobin was 93 per cent and red blood cells 5,640,000. The patient was considerably improved on discharge.

Follow-up. The patient was observed in the Hematology Clinic of the Out-patient Department. His chief complaints after operation were heaviness and occasional pain in the left upper quadrant. Later he began to feel weak and was unable to continue his regular occupation. During the early part of 1936, the hemoglobin and red blood cells began to diminish. Leucopenia and thrombocytopenia became pronounced. A splenectomy was advised but he refused.

On March 1, 1936, about three years after the ligation, there was a recurrence of the gastric hemorrhages. He died before a transfusion could be given.

Comment. For three years following the ligation of the splenic artery the patient felt better. Then there was a recurrence of the symptoms and the patient died after an exsanguination gastric hemorrhage.

III. Osteosclerotic anemia (myelofibrosis or non-leukemic myelosis)

Case 6. Constriction of the splenic artery.

History (Adm. 374955). A. S., a man, aged 53. On February 14, 1933, he was referred for observation by Dr. Samuel Pearl. Symptoms began four years previously with a slight pain in the upper left quadrant where a large spleen was felt. The pain subsided spontaneously and he was apparently free of symptoms until a few months before admission to the hospital. On October 26, 1933, he was admitted to the hospital. He then noted that the abdominal mass had considerably increased in size and he developed a feeling of pressure. He received eight x-ray treatments, which failed to diminish the size of the spleen, or to relieve the pressure. About this time he complained of weakness, headache and frequent nose bleeds.

Examination. Blood examination, following the course of radiotherapy, showed that the anemia had become considerably worse. Hemoglobin dropped to 36 per cent and red blood cells were 1,570,000. A profound leucopenia developed with 600 leucocytes. The differential blood count was said to be normal. After a transfusion of 500 cc. he felt better. Two additional transfusions were given without any effect. He appeared very pale and somewhat dyspneic. The spleen was felt well below the umbilicus.

Laboratory data. The blood picture on February 14, 1933, was as follows: Hemoglobin, 71 per cent; red cells, 3,830,000; white cells, 2,506; platelets, 80,000; non-segmented polymorphonuclear neutrophils, 29 per cent; segmented forms, 34 per cent; myelocytes (neutrophilic), 8 per cent; myeloblasts, 1 per cent; lymphocytes, 24 per cent; monocytes, 4 per cent; monoblasts, 4 per 100 white cells; reticulocytes, 5 per cent; relative cell volume, 29 per cent.

Course. The impression in this case was that of a leucopenic myeloid leukemia. The long-standing history and progressive enlargement of the spleen led us to suspect that the bone marrow may have become sclerotic. A few months later, during the latter part of June, 1933, he complained of pains and aches in the ankles and knees. He found it easier to walk than to sit or lie down. There was some edema of the ankles, but no swelling of the other joints. He noted marked dyspnea on exertion. The abdominal symptoms became more marked. The blood picture remained virtually unchanged. X-ray examination of the bone at this time revealed some rarefaction in some of the bodies of the vertebrae. At the time of admission to the hospital, the spleen could be felt at the antero-superior spine of the ileum. Later osteosclerosis and myelofibrosis were found.

As a result of the work of Payr, this was considered a good case for constriction of the splenic artery for the reduction of the size of the spleen and for inducing a symptomatic improvement, as far as the pain and pressure in the abdomen were concerned.

Operation. On October 30, 1933, a "Drosselung" of the splenic artery was performed under spinal anesthesia. A subcostal left sided incision was made; on opening the abdomen, it was found to be filled in its entirety by the spleen covered by the mesocolon. The splenic artery, coursing along the upper border of the pancreas, was tortuous and about one-half inch in diameter. A band of fascia about one-half inch in width and three inches in length, obtained from the anterior rectus sheath, was placed about in such a manner as to occlude almost completely the lumen of the artery (the fascia was wound about the artery). After completion of this process, no pulsation was felt in the artery to the distal part of the band of fascial application. Although no pulsation could be felt, a small amount of blood was probably coursing through the artery. The accessory spleen in the lesser sac was removed for investigation. A small rent in the mesocolon was sutured and the abdomen was closed in layers.

Postoperative course. After operation, the spleen gradually diminished in size. At the end of a week it was felt at about the level of the umbilicus and later about two fingers below the free border of the ribs. Convalescence was smooth and the general condition seemed improved. On November 30, 1933, he was discharged.

This improvement, however, was temporary, as anemia and weakness became progressively worse and were not influenced by repeated transfusions. The spleen increased in size and again was felt as low as the antero-superior spine.

Second admission (December 1, 1934). A transfusion was given on admission. His condition became considerably worse. A month later, he became dyspneic, edematous and the hemoglobin had fallen to 16 per cent. There was apparently a preagonal leucocythemic leukemic blood picture. Before a transfusion could be given, the patient died.

Necropsy findings. Necropsy was limited to the examination of the bone marrow, liver and spleen through small incisions. There was an absence of true bone marrow, which was replaced by dense fibrous tissue. The spleen presented considerable fibrosis and myeloid metaplasia. There was also some myeloid metaplasia in the liver.

Comment. There was slight improvement only for a short period following operation. The spleen had apparently diminished in size and again attained its former size about six weeks after operation. The "Drosselung" or constriction of the artery did not in any way influence the progressive weakness, anemia and general condition of the patient.

DISCUSSION

A review of the literature shows that ligation of the splenic artery has been carried out in a small series of cases. In some of the early cases the main artery itself was not ligated, but some of its branches instead, and in other instances some of the veins, and in only a few instances has it proven successful.

The first ligation of the main trunk of the splenic artery was successfully performed by Lanz (12) in 1914 for an ectopic spleen. In this instance, the main artery was ligated, and it is likely that the spleen depended for most of its blood supply on this artery alone. This may account for the unusually good result. In other cases the ligation of the splenic artery was followed by necrosis of the spleen, which can be considered virtually a technical splenectomy. In the cases of Banti's disease reported by Blain (3) and Cejudo (6), abscesses developed twenty-one to forty days after operation, requiring incision and drainage.

This operation has also been performed in a few cases of hemolytic jaundice by Alessandri (1), Durante (8) and Valdoni (23). Their results have apparently been successful. Soon after the operation, clinical improvement was noted in all their cases.

Von Stubenrauch (21), in 1922, was the first to suggest the possible substitution of simple ligation of the splenic artery for splenectomy in cases of thrombocytopenic purpura. He reported a favorable result in a man sixty-six years of age with typical symptoms and blood changes of thrombocytopenic purpura. In this case the splenic artery was ligated eight centimeters from the hilum of the spleen. Following this, the patient showed marked clinical improvement. The reaction of the blood platelets corresponded with those observed after splenectomy; there was a marked initial rise and then a return to their former low level. A few of the red blood cells showed the presence of Howell-Jolly bodies, which usually appear after splenectomy. In 1929, Von Stubenrauch (22) published the follow-up of this case, stating that about four years after this operation, there was a recurrence of the purpura which proved fatal. Post-mortem examination showed the spleen to be considerably shrunken and adherent, and it appeared to be of normal consistency. The splenic artery was completely obliterated.

Ligation of the splenic artery for acute thrombocytopenic purpura was performed by Lemaire and D  baisieux (13) in 1924. The vessel was brought through the gastro-epiploic omentum and was ligated at the upper border of the pancreas. Clinical, as well as hematologic improvement was reported. These authors highly recommended this simple procedure and also noted that no particular shock followed the operation when handling the pancreas. They pointed out that the collateral circulation from the inferior pancreatic artery and the left gastro-epiploic artery prevented necrosis.

Van Goidsenhoven (24) reported twelve cases mainly in children, in which ten recovered. No immediate improvement occurred in one case and the patient died several months later from pneumonia. He considers ligation of the splenic artery as the method of choice for this disease. Because the general condition contraindicated splenectomy, Alessandri performed the ligation of the splenic artery in two cases with recovery in only one. Alessandri, always a great advocate of ligation, does not approve of this procedure in purpura as the spleen is usually free and not greatly enlarged and can be removed easily.

An immediate good response may not occur after ligation in contrast to the prompt response following splenectomy. Such a poor result leads to a certain amount of uncertainty so that a secondary splenectomy must be done after the ligation procedure. In two cases of our own series (Cases 1 and 2), ligation of the splenic artery was followed only by transitory good effect, and in both cases a marked recurrence necessitated secondary splenectomy. This was done in one of the cases and was about to be performed in the second case, which terminated suddenly. Likewise, others (Colucci (7), Magendie (14)) have had to follow the ligation by a splenectomy as a result of persistence of symptoms or temporary improvement. Postoperative deaths have also been reported after ligation by Van Goidsenhoven (24), Alessandri (1), Bonanno (4), and Magendie (14). The results following splenectomy for thrombocytopenic purpura may be considered better and remove some of the uncertainty which follows the ligation procedure.

Ligation of the splenic artery seems to offer a less risky procedure in certain cases of congestive splenomegaly (Banti's disease) due to cirrhosis of the liver of various types with or without ascites. It may be indicated or worthy of a trial in advanced cases in poor physical condition. Good results have been reported by Watson (26), Alessandri (1), Marques (16) and Maggiore (15). The latter obtained an excellent result in the ascitic stage.

In such cases operated on by ligation a definite diminution in the size of the spleen followed. In two instances, the patients survived one year (Cases 3 and 4) and one case for three years (Case 5). In the latter case the ascites subsided for two years. In all these instances as a result of the marked liver damage, these patients would have been poor risks for splenectomy. It must be pointed out in Case 4 that the recurrence of the gastric hemorrhages a year after operation served as an indication for a secondary splenectomy. Following the operation the patient developed pneumonia, as a result of his poor physical condition, and died.

Ligation of the splenic artery has not been carried out often in cases where the spleen has reached an abnormally large size, especially Gaucher's disease. There is a possibility that such an operation may be followed by extensive abscess formation as a result of the necrosis as reported by Blain

(3) and Cejudo (6). The substitution of fascial constriction, as suggested by Payr (18), may become of some importance in an attempt to shrink the enormous spleen, as occasionally encountered in leukemia, polycythemia and Gaucher's disease. As splenectomy cannot be considered curative in such instances, Payr's method of fascial constriction may prove to be worthy of consideration; in fact, Payr has carried out this method with apparent success in four cases. The vessel was approached through the gastro-epiploic omentum. The artery may be thus localized. A piece of fascia, $1\frac{1}{2} \times 14$ cm., obtained from the rectus sheath was employed as the ligature. Alessandri (1) employed this operative procedure in four cases; there was one fatality but no influence on the course of the disease in the three others.

SUMMARY

1) Ligation of the splenic artery was performed in two cases of purpura hemorrhagica, three cases of splenomegalic cirrhosis of the liver, and a constriction, or "Drosselung," in one case of osteosclerotic anemia.

2) The clinical and hematological results varied considerably. No marked clinical or hematological changes were noted in the purpura hemorrhagicas; no improvement of the condition of two cases of congestive splenomegaly or splenomegalic cirrhosis of the liver, although in the third case the ascites subsided and some improvement took place, in all three cases there was recurrence of hemorrhages within a few months to a year following the operation.

3) Appreciable diminution in size of the spleen was obtained in only two cases.

4) Follow-up of all cases indicated that except in some instances of congestive splenomegaly results did not warrant the continuance of such a procedure as a substitute for splenectomy. Splenectomy is far superior, or at least removes the element of uncertainty which sometimes accompanies a ligation of the splenic artery.

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ECHINOCOCCUS CYST OF THE LIVER: PROLONGED COURSE WITH OPERATIVE REMOVAL AND COMPLICATING THROMBOSIS OF PORTAL VEIN

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[From the Services of Dr. B. S. Oppenheimer and Dr. R. Lewisohn]

Hydatid cysts occur in the liver in much higher incidence than in all other organs combined. This predilection (about 60 per cent) is obviously due to the fact that the liver is the recipient of the blood flow of the portal system and hence of infective material from the intestinal tract. The presence of a large unilocular hepatic cyst is usually manifested by a palpable mass or, with multiple cysts, by an irregular or nodular liver. Diagnosis is aided by knowledge of the geographic distribution of the disease and its epidemiology, a history of chance exposure to infected intermediate hosts, chiefly the dog and sheep, eosinophilia of the blood, or recovery of *echinococcus granulosa* from the intestine. In the absence of any of these features, hydatids may achieve considerable size before arousing suspicion of their presence. In cysts of long duration the tendency to calcific deposits between the external laminated cuticle and the internal parenchymatous layer may provide roentgen evidence of their presence. The case to be presented puzzled clinicians for more than four years. During this time two exploratory laparotomies and exhaustive laboratory studies failed to disclose the basis for the bizarre and disabling symptoms. The ultimate roentgen visualization of an oval calcified area in the liver finally established the diagnosis.

CASE REPORT

History (Adm. 269441). A 33 year old white man, a native of Poland, was admitted to The Mount Sinai Hospital on May 17, 1926, with a four months' history of recurrent attacks of epigastric pain, pyrosis, intense weakness and moderate weight loss. His parents and nine siblings were apparently free of disease. He had been married for thirteen years and had two healthy children. He was engaged in the manufacture of celluloid novelties requiring long hours of exacting work. In 1918 an appendectomy was performed. In 1920 he was confined to bed for four months with a severe attack of rheumatic fever; valvular heart disease was subsequently detected. Exertional dyspnea, palpitation and vague precordial pain occurred intermittently, chiefly in cold weather. He did not smoke or use alcohol. Three years before admission he had a brief episode of epigastric pain similar to his current attacks. Following this he was entirely free of pain until the onset of the present illness four months before admission. The onset of this illness took the form of a sudden attack appearing two hours after a heavy meal and characterized by intense colicky pain radiating from the epigastrium to the sternum, to both shoulders and to the

interscapular region. Subsequent attacks, which appeared with increasing frequency, lasted from 15 to 20 minutes and were associated with sour eructations which gave relief. He had no vomiting, nausea, jaundice or hematemesis. A week before admission, after eating a large meal, he was suddenly seized with violent generalized abdominal pain; he collapsed in the street and was taken to Bellevue Hospital. Prompt relief followed hypodermic medication and he left against advice. Dull epigastric pain persisted, however, reaching its greatest intensity about an hour after meals. He lost about 20 pounds in the four months of the present illness, largely due to voluntary restrictions and impaired appetite.

Examination: Despite his weight loss, he appeared adequately nourished, and was in no apparent distress. His pupillary reactions were normal; the fundi were negative. The area of cardiac dullness was slightly increased to the left with the apical impulse palpable 10 cm. to the left of the midsternal line in the fifth interspace. A presystolic crescendo murmur was audible just within the cardiac apex and was followed by a snapping first sound; the pulmonic second sound was distinctly accentuated. The blood pressure was 95 systolic and 65 diastolic. On fluoroscopy, the heart disclosed distinct prominence of the pulmonic conus with some dilatation and hypertrophy of the left auricle. The lungs appeared negative. There was well marked tenderness, but no rigidity, in the epigastrium and right hypochondrium. A soft mass which simulated the gall bladder and descended with inspiration extended 3 cm. below the apparently enlarged right lobe of the liver.

Laboratory Data: Blood: hemoglobin 86 per cent; leucocytes, 7,800; polymorphonuclear neutrophils, 53 per cent; lymphocytes, 37 per cent. The urine was negative. The stools revealed no occult blood. On biliary drainage, light brown turbid fluid was obtained, alkaline in reaction; microscopic study showed numerous epithelial cells, a few leucocytes but no cholesterol crystals. Roentgen examination both with and without the dye failed to visualize the gall bladder. The electrocardiogram disclosed right axis deviation with some prominence of the P waves.

Course: His symptoms rapidly diminished and in a few days he was discharged with a diagnosis of chronic cholecystitis with pericholecystitis and rheumatic cardiovascular disease with mitral stenosis.

Second Admission: He was readmitted on June 8, ten days later, complaining of a recurrence of severe right upper quadrant pain, pyrosis and sour eructations. Although there had been no acute attack, and no fever, chills or jaundice, the distress had become more intense. Examination disclosed distinct tenderness and muscle spasm in the region of the gall bladder; the suggestive mass, previously described, was no longer felt. In the light of the unremitting nature of his discomfort, it was felt that exploration was indicated.

Operation: The gall bladder was neither enlarged nor thickened and no stone could be felt; it was situated, however, low in the liver bed and surrounded by adhesions to both liver and duodenum. The tissues bled freely and there was an unusually large amount of oozing from the liver bed. Mobilization and removal of the gall bladder were difficult on account of its depth, with dissection begun at the fundus and continued toward the cystic duct. The common duct could not be adequately explored as most of the oozing occurred during this procedure. There was a moderate degree of postoperative shock and considerable bleeding from the wound. Several transfusions were required. Pathologic study of the gall bladder revealed "chronic inflammation."

Third Admission (June 12, 1929): Interval History: The patient was completely asymptomatic for about one year when attacks of epigastric pain recurred. Jaundice appeared during one relatively mild episode and operation was advised at another hospital. The pains were now described as beginning with an intense burning sensation in the epigastrium succeeded in a few minutes by lancinating pain

which radiated to both shoulders, lasting intermittently from one to two hours and leaving him completely exhausted. On the night preceding admission, after consuming several cold drinks, he became nauseated, vomited and had violent epigastric cramps. This attack was associated with severe dyspnea and palpitation.

In view of the recurrent episodes of right upper quadrant pain following cholecystectomy, the presence of a common duct calculus was deemed likely and an exploratory choledochotomy was performed under spinal anesthesia. There were many adhesions binding the stomach to the anterior parietes and the duodenum to the under surface of the liver; the common duct was not dilated and no stone was felt. The pancreas was firm and nodular and the liver appeared slightly enlarged. The intra-abdominal adhesions were divided and the abdomen was closed. The icterus index, which had been 55 on admission fell rapidly to 12. He had numerous mild attacks of epigastric pain following operation, but was discharged apparently improved on July 1, 1929.

Fourth Admission (July 20, 1929): *Interval History*: Two days following his discharge he had another violent attack of epigastric pain accompanied by jaundice. The distress persisted in diminishing intensity until his admission.

Examination: There was a diffusely tender area in the right upper quadrant at times suggesting the presence of a mass, which moved with respiration; it did not fluctuate, and felt distinctly intra-abdominal with its right border apparently continuous with the right lobe of the liver. The spleen was not felt. There was no hepatic shock or costovertebral tenderness. The skin had a diffuse icteroid tinge. In the light of the persistence of the symptoms, intermittent jaundice and the negative findings at two explorations, it was felt that either a subacute hepatitis or cholangitis lenta was present.

Laboratory Data: Icterus index, 12; sedimentation rate, 30 minutes; blood platelets, 500,000. Dye test with bromsulfalein showed abnormally high retention in 30 minutes: Van den Bergh direct test showed delayed positive reaction, and indirect reaction positive 1 to 100,000 being equivalent to 1 mg. of bilirubin per 100 cc. There were no leucine or tyrosine crystals in the urine.

Following some amelioration in his symptoms he asked to be discharged on July 31, without, however, manifesting any objective change.

Fifth Admission (December 9, 1929): Following his discharge from the hospital in July 1929, he had two more attacks of violent right upper quadrant colicky pains associated with jaundice.

Examination: The liver was palpable with diffuse tenderness in the right upper abdomen and moderately deep icterus. The stools contained urobilin; bile was obtained on biliary drainage. Although the interpretation of this bizarre clinical picture remained obscure the chief hypotheses were: 1) intermittent exacerbations of a chronic pancreatitis with swelling of the head of the pancreas and consequent compression of the common bile duct; 2) recurrent catarrhal duodenitis with retrograde extension of low grade infection into the duct and 3) a mild streptococcus viridans infection of the biliary passages. Following the institution of two-hour duodenal lavages with warm Carlsbad salts he improved rapidly and the icterus disappeared. He was discharged on December 16, with instructions for self-administration of drainage. The clinical picture was not clarified.

Sixth Admission: The abdominal pain had attained such severity that the patient demanded relief even at the cost of further operation. Jaundice had recurred intermittently; the temperature course had been subfebrile. There was direct and rebound tenderness over the entire right upper region of the abdomen. Finally the long standing mystery surrounding this patient's inexplicable clinical picture was resolved by an abdominal roentgenogram. This disclosed a large spherical area of calcification about 5 inches in diameter in the region of the right lobe of the

liver which strongly suggested intrahepatic echinococcus cyst (fig. 1). The skin reaction to echinococcus antigen was strongly positive. Liver function tests revealed evidence of moderate hepatic damage. As it was felt that the presence of the cyst accounted for all of his bizarre symptoms, it was decided to attempt its removal when the jaundice had subsided.

Operation (Dr. Richard Lewisohn): On February 3 the first stage of a trans-diaphragmatic exposure of the cyst was performed under gas-oxygen anesthesia. The diaphragmatic approach was deemed advisable as marsupialization through the abdominal route was not thought feasible. Following resection of the tenth rib, the pleura was inadvertently entered and the diaphragm was, therefore, sutured to the pleural opening. The diaphragm, which was at no point adherent to the liver, was secured to the pleura of the chest wall by interrupted sutures and the wound packed with iodoform gauze.

The postoperative course of this preliminary operation was uneventful and there was rapid expansion of the right lung. A week later, the actual drainage of the cyst was undertaken. Under local anesthesia part of the eleventh rib was resected to



FIG. 1. Calcified hepatic cyst

secure more adequate exposure. The diaphragm was incised, a needle introduced into the cyst, and turbid fluid was aspirated. On incising the cyst, a large quantity of purulent fluid containing numerous daughter cysts was evacuated. A large tube was introduced through the opening to maintain drainage.

Course: For the subsequent few months drainage was constant. A roentgenogram taken three weeks after operation disclosed considerable diminution in the size of the cyst. Subsequent films, at monthly intervals, failed to indicate further contraction. During this period he showed progressive improvement and there was no recurrence of either abdominal pain or jaundice. He was discharged on May 2, 1930, with the drainage tube *in situ*.

Seventh Admission: (September 7, 1930). For a week preceding admission the reappearance of epigastric and right upper quadrant pains suggested the need of further study. The sinus had been discharging considerable quantities of sero-sanguinous material. The region of the scar was exquisitely tender but there was no rigidity. He was discharged September 9, but he was urged to return at a later date for total enucleation of the cyst.

Eighth Admission (September 12, 1930): The patient was admitted for operative revision of the echinococcus cyst of the liver.

Operation (Dr. Richard Lewisohn): Following excision of the scar, the eleventh rib was further resected in its proximal part for about 2 cm. During this procedure a small opening in the pleura was accidentally made and closed by three interrupted catgut sutures. The cavity of the cyst was small, barely admitting one finger, and lined with calcareous masses. After an unsuccessful attempt to separate these masses with the curette, the lining was partly removed by blunt dissection. It was not deemed advisable to complete the procedure in one sitting and the distal part of the cavity was left *in situ*. A large Mikulicz dam was inserted into the cavity with several packings.

Postoperative Course: Aside from moderately profuse oozing, the postoperative course was uncomplicated. Six weeks later, on November 10, 1930, the second stage was performed. The cyst was removed in 3 pieces, partly by dissection and partly by manual separation from the surrounding liver tissue. It was felt certain that the entire cyst (fig. 2) had been removed. There was very brisk bleeding from the liver bed. The postoperative reaction was severe due to prolonged and almost intractable oozing. Profuse biliary drainage persisted for some time. Subsequent

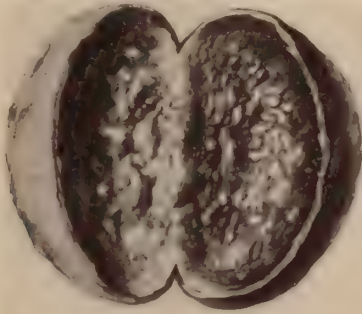


FIG. 2. Echinococcus cyst of liver, reconstructed. (Courtesy of Dr. Richard Lewisohn.)

improvement was rapid, however, and he was discharged, apparently comfortable, on December 30, 1930.

Ninth Admission (April 3, 1931): He was readmitted to the Medical Service because of increasing exertional dyspnea and palpitation, orthopnea and pretibial edema of two weeks' duration. He was found to be in moderate congestive heart failure. The heart was distinctly enlarged and presented a mitral configuration on fluoroscopy. A few moist râles were audible at the right pulmonary base. A loud crescendo presystolic murmur was audible in the third and fourth left parasternal zone and the pulmonic second sound was snapping in quality. The blood pressure was 100 systolic and 64 diastolic. The electrocardiogram disclosed left axis deviation and an inverted T III. The liver and spleen were not felt.

Laboratory Data: Cholesterol, 165 mg.; ester, 40 mg. per cent. Van den Bergh, direct, negative; indirect, 1:50,000 (bilirubin, 0.5 mg.). Blood proteins: albumin, 4.7 per cent; globulin, 2.0 per cent; total 6.7 per cent. The urine revealed a trace of urobilin.

Course: Following a week of bed rest with fluid restrictions, he improved rapidly and was discharged on April 11 with instructions to limit his physical activity. He had no symptoms referable to the echinococcus disease.

At the Follow-Up Clinic on October 28, 1931, he was completely asymptomatic and had gained 25 pounds in weight.

Tenth Admission (November 15, 1931): He was readmitted to the Surgical Service

because of intermittent right upper quadrant pain and nausea of several days' duration. The examination did not disclose any significant findings and with the cessation of discomfort on the day following admission he was discharged.

A roentgenogram of the abdomen on March 25, 1932 disclosed no evidence of calcification in the hepatic region.

Eleventh Admission (September 21, 1932): *Interval History*: He had been entirely free of discomfort until four weeks before admission when sharp pain in the right upper quadrant suddenly appeared. He was removed to another hospital where the pain was promptly controlled with morphine. Operation was advised but refused. The pain, accompanied with the vomiting of bile, recurred five days before admission.

Examination: His nutrition was excellent, skin color good, and he was in no apparent discomfort. There were, however, numerous bizarre seizures, almost daily in occurrence, which were at first interpreted as hysteria. The episodes were heralded by the emission of a sound similar to the whinnying of a horse for several minutes while he clutched at his precordium. He failed to respond to questioning or to painful stimuli except by fluttering of the eyelids. The pulse became rapid and the blood pressure rose to 160 systolic and 90 diastolic; consciousness was apparently lost. The seizures generally averaged 15 minutes in duration and were followed by a sense of extreme weakness. He denied any memory of the attacks. He was transferred to the Neurological Service where more detailed studies of the attack were made. It was observed that with the quivering of both eyelids, the eyeballs jerked forward synchronously about 120 times a minute; the pupils reacted to light; the patellar and ankle jerks were active and equal; the left superficial abdominal reflexes were diminished. Plantar stimulation elicited no response on either side. Ten minutes after the attack the right palpebral fissure was wider than the left; both internal recti seemed weak; the tongue deviated to the right; the left side of the soft palate was apparently lower than the right; the right knee jerk was more active than the left.

Course: It was felt that a metastatic echinococcus cyst in the third ventricle in the region of the quadrigeminal plate might explain the clinical picture. His patently psychoneurotic behavior, however, and the inconstant and specious sensory changes tended to militate against the possibility of a focal lesion in the central nervous system. His subsequent peculiar behavior strengthened the concept of a psychoneurosis with extreme suggestibility and hyperreaction. During his period of observation on the Neurological Service, the blood eosinophiles never exceeded 4 per cent.

With recurrence of the right upper abdominal pain he was admitted to the Montefiore Hospital on April 10, 1933. There was a moderate secondary anemia but no eosinophilia. An abdominal x-ray examination following intravenous thorotrast revealed the liver distinctly outlined and approximately normal in size; the spleen was slightly enlarged. Further roentgen studies, following the injection of air into the peritoneal cavity, disclosed numerous adhesions attaching the liver to the surrounding structures. All other laboratory studies were negative. Although he experienced no recurrence of the pain while in the hospital, he had numerous hysterical seizures and displayed persistent emotional instability.

Twelfth Admission (October 15, 1935): After a period of 18 months of relative comfort, severe epigastric pain with midscapular radiation recurred and was followed during the three weeks preceding admission by three large hematemeses and tarry stools. Jaundice had been absent.

Examination: His nutrition was good but his behavior was distinctly psychoneurotic. The left upper lid was ptosed; pupillary reactions were normal. The abdomen was soft and there was no visible evidence of collateral circulation. There

was a very tender protruding right lumbar incisional hernia containing intestine. The liver descended 3 cm. below the costal margin and was quite tender. A firm spleen descended 2.5 cm. There was no detectable ascites or scrotal varicosities. There was moderate clubbing of the fingers and toes. The blood pressure was 104 systolic and 76 diastolic. A neurologic survey disclosed a right Horner syndrome, nystagmoid movements of the eyes, facial asymmetry and unequal knee jerks. These were interpreted as due to a residual process, probably encephalomyelitic in nature. His prolonged illness apparently served as a specific psychogenic background accounting for the extreme overflow of pain stimuli.

Laboratory Data: Blood: hemoglobin, 80 per cent; red blood cells, 4,350,000; platelets, 150,000; white blood cells, 2,400 with non-segmented polymorphonuclear leucocytes, 8 per cent, segmented, 51 per cent; lymphocytes, 31 per cent; monocytes, 6 per cent; eosinophiles, 4 per cent. Roentgen gastro-intestinal studies with special reference to the esophagus disclosed the presence of many large esophageal varices (fig. 3); the duodenal bulb was drawn far up into the right upper quadrant by adhesions; the liver appeared small; the spleen distinctly enlarged.



FIG. 3. Esophageal varices

Course: In the light of the enlarged spleen, recurrent hematemeses, leucopenia, thrombocytopenia and esophageal varices, the diagnosis of splenic or portal vein thrombosis was considered probable. The history of repeated, although remote, attacks of jaundice, suggested either an independent or associated hepatic cirrhosis. The patient was discharged on October 27, 1935 with his condition essentially unchanged.

Thirteenth Admission (June 3, 1937): Interval History: Following his discharge in October 1935, the patient remained chronically ill, suffering with abdominal pain of variable intensity, at times almost inducing collapse. Relief was secured by increasing quantities of morphine. There was no nausea, vomiting or diarrhea. Episodes of hematemesis, amounting to 6 to 12 ounces of dark red blood appeared every 3 or 4 months. Following the vomiting of over a quart of blood one month preceding admission, several transfusions were administered at another hospital. Bleeding recurred almost immediately after his discharge. With persistent bleeding, progressive enlargement of the abdomen, orthopnea and ankle edema, he was readmitted to the Medical Service.

Examination: He presented a ghastly pallor and moderate air hunger, and was

still vomiting blood; he barely responded to stimuli. The heart rate was rapid, 130 beats per minute, and the sounds were muffled. There was considerable ascites and well marked ankle edema. The blood pressure, at first unobtainable, rose after 3 transfusions to 60 systolic and 40 diastolic; he remained in shock for about 24 hours.

Laboratory Data: Blood: hemoglobin, 29 per cent; red blood cells, 1,600,000; white blood cells, 9,000 with 90 per cent polymorphonuclear leucocytes, 6 per cent monocytes, 3 per cent lymphocytes and 1 per cent myelocytes; platelets, 30,000. The clotting time was 1 minute; bleeding time, 3 minutes; clot retraction was normal. The blood urea nitrogen was 25 mg. per cent; glucose, 175 mg. Icteric index, 3. Total proteins, 4.9 per cent. The urine contained occasional leucocytes, red blood cells and granular casts. The stool reaction for blood was strongly positive. The electrocardiogram disclosed low voltage in all leads.

Course: Following six transfusions in the course of four days he showed some improvement. Diffuse bronchopneumonia developed and he was placed in an oxygen tent. On the fifth day the abdominal distention increased, extreme tenderness appeared in the right upper quadrant, and a distinct fluid wave with shifting dullness in the flanks was detected. The blood platelet count had fallen to 35,000. Mesenteric thrombosis was suspected and abdominal puncture was performed. A free flow of serosanguinous fluid resulted. With the resolution of the bronchopneumonia and cessation of the bleeding, improvement was gradual with a rise of hemoglobin to 56 per cent, a rise of blood pressure to 110 systolic and 68 diastolic, and of platelets to 50,000. Blood disappeared from the stools and edema and ascites rapidly diminished. On the eleventh day, while at rest, he suddenly vomited about 1500 cc. of blood and went into collapse. Despite transient improvement after repeated transfusions, he lapsed into coma, air hunger reappeared, his temperature rose to 106° F. and he expired three days later.

Necropsy Findings: The abdomen was greatly protuberant with marked bulging in the flanks due to the presence of over 4000 cc. of amber-colored fluid. The lower borders of the liver and spleen did not extend below the costal margins. There were numerous omental adhesions to the old cholecystectomy scar and to the region of the *porta hepatis* as well as to the hilus of the spleen. The omentum contained many distinctly dilated vessels. There was a great deal of fat about the *porta hepatis* and pancreas. The left lobe of the liver was greatly shrunken and attached by adhesions to the diaphragm; these adhesions contained numerous vessels. The postero-lateral surface of the liver was firmly adherent to a dense mass of connective tissue which was at least 5.0 cm. in thickness; this was in turn adherent to the operative scar. The superior surface and a portion of the posterior surface of the liver were firmly adherent to the diaphragm. *Thorax:* There was a small amount of clear colored fluid in the pleural cavity. The base of the right lung was firmly adherent to the right dome of the diaphragm. There were scattered firm pleural adhesions over the three lobes of the right lung. *Lungs:* There was intense hyperemia throughout. The trachea and bronchi were deeply injected and full of frothy sanguinous fluid. The pulmonary arteries and veins showed no unusual features. *Heart:* Enlarged, weighing 360 gms. The right auricle was dilated and hypertrophied. The endocardium was smooth. The right ventricle was moderately dilated and enlarged. The mitral leaflets were diffusely thickened. There was delicate shelf formation and gross vascularization. The leaflets were slightly fused with straightening of the insertion of the chordae tendinae. The latter were all considerably thickened. A few grayish-red verrucae were present on the line of closure of the anterior leaflets. The cusps of the aortic valve were all thickened with marked fusion at the commissures. There was a grayish-red verruca on the semilunar fold of the posterior cusp. There was an accessory right coronary ostium. The coronary arteries disclosed only scattered yellowish intimal streaks. *Liver:* The liver was very small and weighed

approximately 1100 gms. The diaphragm and fibrous scar tissue were adherent to the right lobe. The left lobe was represented by a tongue-like projection about 10 cm. in length, 5 cm. in width and 2 cm. in thickness. Where no adhesions were present, the capsule was smooth and thin. The underlying parenchyma had a definitely brownish tinge. The right lobe was also small and deformed in the posterolateral position. Section through the scar tissue in this area revealed its extension to within 3 cm. of the main portal vein before liver parenchyma was encountered. Within the scar tissue were many large vessels and some bile ducts. No gross evidence of echinococcus cyst disease was seen. Another section through the right lobe of the liver revealed a dirty-brown moist parenchyma. The normal architecture was not easily discernible. The central zones were indistinctly visualized as grayish-red areas. The portal areas appeared enlarged and were grayish-white and fibrous in appearance. The larger bile ducts were all dilated. Section through the left lobe of the liver showed a similar picture except for the deep red congested appearance of the central zones. The hepatic arteries and veins showed no unusual features. *Portal Vein:* This was the seat of extensive disease. Beginning at its origin in the splenic area there were many cord-like thickenings of the intima and web-like bands which split the lumen into septa. A similar but not so extensive change was present in the superior mesenteric vein. In addition, in the superior mesenteric vein, about 2 cm. from its junction with the splenic vein, there was a reddish-gray somewhat friable mass, 2 cm. in length, projecting about 10 mm. into the lumen. Within the portal vein about 2 cm. from the junction of the splenic and superior mesenteric veins there were a number of web-like bands, similar to those described, which prevented the penetration of a probe. After section above this point the portal vein could be picked up again and showed a lumen about 1 cm. in diameter. Into this lumen entered a greatly enlarged superior pancreaticoduodenal vein and a distinctly dilated coronary vein. Two centimeters further along in the portal vein there was a sac-like dilatation with occlusion. The portal vein within the liver was of normal size and on probing toward the *porta hepatis* the obstruction described was encountered. The gall bladder was absent. The common and hepatic ducts were dilated and thickened. The papilla of Vater was prominent and no obstruction was encountered. *Spleen:* The spleen was moderately enlarged, weighing 425 gms. It was purplish, flabby and the capsule was wrinkled. On section it was diffuent and the trabeculation definitely increased. The Malpighian corpuscles could not be easily identified. There were numerous minute hemorrhagic areas throughout. The radicles of the splenic veins were not unusual. The splenic arteries appeared normal. The short gastric veins were dilated and distended. *Pancreas:* The pancreas was markedly infiltrated with fat. The ducts were not dilated. The *kidneys* were essentially normal. *Esophagus:* The esophagus was extremely edematous, particularly in the submucosal layer. There were a number of large varices in the lower and middle third. Just adjacent to its junction with the stomach there were two small grayish-white projecting masses with black centers which surmounted varices. *Stomach:* The stomach showed congestion of the mucosal vessels and dilatation of the short gastric veins. The coronary vein and its branches were also dilated and distended. *Intestines:* The small intestines showed no unusual features. There was a large quantity of clotted blood in the colon and rectum. There were no points of bleeding throughout the large intestine and the mesenteric vessels were not remarkable.

Microscopic: Liver: The lobules were atrophied and the cords and sinusoids narrowed. The portal vein was completely obliterated in most of the fields; in others, it was widely patent. The hepatic arteries were small and appeared narrow. The section through the right lobe of the liver disclosed considerable scarring and a large mass of dense collagenous tissue. There were numerous areas of atrophy of liver

cells in the adjacent lobules. Centrolobular congestion, atrophy and necrosis were distinct. The section through the occluded portal vein and its entrance into the liver showed complete fibrotic obliteration with recanalization. *Portal Vein*: The section taken near the hilus of the liver showed a dense fibrous thickening of the intima. *Splenic Vein*: A section taken about 6 cm. from the hilus of the spleen showed a projecting nodular fibrosis with thickening of the intima and vascularization.

COMMENT

The appearance of hydatid disease in a man who has lived in this country for the greater part of his life with no known exposure to an intermediate host, is worthy of note. Epidemiologic study of sporadic cases has been successful as a rule, in tracing a specific exposure or in unearthing a history of residence in a district where the disease is endemic. No such facts were noted in this case. Additional features of interest were the persistent absence of eosinophilia during the eleven years of observation, the roentgen appearance of calcification of the cyst wall as the first hint of its presence, and the failure of dissemination of secondary hydatids in spite of prolonged opportunity.

The removal of the cyst which occupied the greater part of the right lobe of the liver involved extensive trauma to the surrounding parenchyma with the development of dense postoperative adhesions. These factors contributed to the eventual thrombosis of the portal and splenic veins. Recanalization of the thrombi accounts for the unusually long survival.

The bizarre neurological picture which, for a time, suggested metastatic echinococcus cyst of the third ventricle in the region of the quadrigeminal plate, proved to be the peculiar manifestations of an hysterical response to suffering which had become intolerable.

SUMMARY

1. A huge solitary hepatic echinococcus cyst eluded diagnosis until calcification of its wall permitted roentgen identification.
2. The cyst was completely excised after a series of hazardous procedures. There was unavoidable trauma to the surrounding tissues.
3. Portal and splenic vein thromboses ensued and the patient finally succumbed several years later to exsanguinating hemorrhages from esophageal varices.

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SELECTIONS FROM THE NOTEBOOK OF A HOSPITAL ADMINISTRATOR¹

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The clinician entering the office of the hospital administrator carries within his personality an organizational problem which has a direct as well as an indirect relationship to the agenda of their meeting. Whatever it may be that troubles him and requires, in his opinion, administrative assistance, his very presence is proof that hospital administration is a cooperative undertaking. The *summon bonum* in hospital administration is the one in which the clinician has an understanding attitude toward administrative technique and in which the administrator has an understanding attitude toward clinical procedure, leading to mutual respect and productive effort. Failure on the part of hospital administrator and clinician to understand each other fully and to pull together in the common interest, may prove to be an insurmountable barrier to hospital progress, and therefore to scientific progress.

Assuming that the governing authorities have given the medical staff an administrator who will have their respect, there will still be some handicaps which they will have in the presence of each other. For this reason, a certain amount of adjustability must be exhibited on both sides. The administrator who lives up to all of the requirements of inspired leadership may expect to be looked upon at times, and particularly by those who chafe under restraint, as the symbol of oppressive rules and regulations. For this situation there is no complete and infallible remedy. The administrator who would protect his office from the demoralizing inroads of the unfriendly critic, must be willing to make frequent clear statements of policy and explain matters patiently, while reserving the right to withhold premature comment. The intelligent hospital administrator knows the depths of the sea in which he is sailing and, if he is in doubt, takes occasional soundings to make sure. Like the captain of a ship at sea, he fears the fog more than he fears the storm.

One of the essential requirements of the hospital administrator is the gift of vision or, in lieu of this, the gift of seeing and making practical use of vision in others. In parlous times like these, however, the clinician must be easy with his judgments and must not expect too much from the

¹ A discursive glance at patient, administrator, philanthropist, physician, social worker and lay employee.

administrator. Visibility is poor, the ceiling is low and there are storm clouds in all directions, some of them no larger than a man's fist as yet. At the moment very few social workers can see beyond their own noses.

The clinician must not lose his balance when he finds the hospital administrator at times inaccessible. Time is a limited and often intangible determinant. Obviously one cannot personally conform with the ideas of every last member of the working staff on all occasions. Like every executive, the administrator must discover ways and means of making the best use of his day. His intra-mural life consists in large part of correspondence, written and oral. "Put it in writing" seems almost like a command performance at times. Personal interviews, which offer more room for expansion, are, therefore, more eagerly sought. They are at least as useful as written correspondence in revealing the mind of the petitioner. A few examples might here be cited.

Take, for instance, the gentleman who calls to exchange a few pleasantries, scatters a few flattering remarks and, after a while, often a long while, retreats courteously to the door where he discovers that he has forgotten something ("Oh, by the way . . .") The postscript, so to speak, turns out to be the essential reason for the visit, though you would seldom guess it, his manner having been so thoroughly smooth and disarming. If the administrator is on the alert, reason will prevail and the interests of the hospital will be protected. If not, he wins, having put something over painlessly as well as successfully. Beware of the visitor who does not wear his motives on his sleeve.

Another type is the one who might be described as a time-waster. When, to be courteous, we ask him how he feels today, he takes us seriously and goes into great detail. Our eyes shift upward tactfully to the clock on the wall, with an innocent look which indicates that time may be flying for one of us if not for the other; but he goes on, even though he promised to take "only a few minutes" of our time. This is the visitor on whom time hangs heavily, so heavily in fact, that he can neither understand nor appreciate an appointment system. He just happened to be in the neighborhood and thought that he might take the opportunity of dropping in and talking things over. Oftentimes he is too important to be turned away. One case in this category, who requires delicate treatment, is the one who has time as well as money to spend and forgets for a long moment the importance of good budgeting habits.

Nor do our troubles end with face to face experiences like these. One of the telephones hard by might go into action at any moment, however embarrassing that moment might be. Again "I'll only take a minute of your time" and we paw the ground impatiently, forgetting that it might have been worse. An efficient secretary, personal tact, a good sense of timing, and the ability to speak gently as well as diplomatically, must all be combined and brought into play, if matters are to be expedited. "Put

it in writing" is helpful, especially if one is not a good listener, but "drop in and let's talk it over" is, after all, desirable, if one is eager to escape the accusation of unapproachability.

Our petitioner is not, as a rule, as efficient as we are in the employment of time to the best advantage. Moreover, he is sure that his case grows stronger as he multiplies his reasons. He is under an emotional strain at times and does not see the woods for the trees. One must, therefore, hold on to himself while remembering that optimistic remark of Goethe "We are not unhappy—we are only impatient."

The administrator must be careful with his judgments and decisions, for one seldom gets all the facts. He does, indeed, begin life with a handicap. Unlike the worker in the exact sciences, he cannot hope to be governed completely in his decisions by a repetition of similar cases occurring in series. ("Hard cases make bad law.") He must often say "no" when he wishes with all his heart that he could say "yes." He must protect the interests of the group, while bearing the needs of the individual in mind. He is hampered by rules and regulations which, paradoxically, are largely of his own making. He knows that the tendency to lay down policies, to make rules and regulations, to develop schemes of organization, and then to adjust patients and personnel to them is bound to defeat the purpose of the hospital in the long run.

The greatest blessing that could be vouchsafed to the sick who are confined to the wards of a hospital, is the personal interest of the hospital administrator in the bedside, for that is where the lessons in humanity are to be learned. In the larger hospitals the administrator is overwhelmed at times by "paper-work" which puts an unreasonable burden on him and compels him to give more attention to the business departments of the hospital than to the professional departments which are of more immediate concern to his patients. Many mistakes occur in the wards before they come to the notice of the administrator, who lends encouragement to their repetition if he is addicted to vicarious methods of administration. No one knows better than the executive that there is more to the administration of a hospital than may be seen from his office and that there is a difference between arm-chair and bedside administration. "The letter killeth" in hospital administration, as in all other forms of human administration.

If the administrator could be as much concerned with mistakes in the wards as he is with those that occur in the business departments, hospitals would be farther ahead on their path of communal service. The contrast between the neglect of the clinical audit and the uniform insistence upon the periodic financial audit is striking. It is one of the paradoxes of hospital administration that far more attention is paid to the fuel that goes into the boiler than to the food that is to sustain or restore the patient, for whose sake the hospital and its power plant have come into existence.

Perhaps this is because the results of failure are more tangible in the first case than in the second. The inanimate machine does not complain; it simply stops working. It is a major task in itself to make sure that the right patient receives the right dose of the right medicine at the right time.

In his dealings with the medical staff the hospital administrator is dependent, to a large degree, on the governing authorities. The character of the trustee is a good measure of the quality of the hospital. Men who maintain high standards of business and private life can be depended upon to maintain equally high standards in philanthropic activities for which they share responsibility. Charitable institutions like these deal with no stockholders, no commercial profits, no dividends and no merchandise other than human suffering which must be relieved by charity in its broadest sense. While the business affairs of a hospital may show a surplus or a deficit, in scientific affairs there is always a deficit and never a surplus. (Note Goldwater: "A deficit is often the symbol of a noble ambition.")

Vested interests belong in a different category. The trustee who, in good faith and with the best intentions in the world, becomes addicted to a hobby in the hospital must not complain when he is reminded that his "baby"—as some of them fondly call it—may be throwing the budget out of balance. Philanthropy is at its best when full confidence in the impartiality of the governing board brings gifts that have no strings attached to them.

We have no contract with philanthropy—only a gentleman's agreement. The hospital administrator and clinician must, therefore, join hands for the purpose of maintaining a philanthropic establishment which is convincing, and worthy of the charitable hearts that maintain them. To some departments of the hospital it is given to make a larger contribution than to others. The coldest of laboratory investigators must admit that the social service department which, though it came later, may be considered the spiritual ancestor of the modern hospital, is the conscience of the hospital. To this department the staff physician must be willing to come for whatever help it can give in bringing about a cure for the patient. Medication for a given patient may or may not prove to be remedial. The surgical operation may or may not prove to be successful, but medical social service, without exception, always produces beneficial results and its place in the hospital budget should therefore be safeguarded.

Patience is more frequently a characteristic of the social service department than it is of the clinical departments of the hospital—which prompts me to add that the true humanitarian never becomes reconciled to suffering. Medical social service is a modern concept. Not so long ago it belonged body and soul to the field of "charity." We have changed the name, but not the object of this department. The "department of social welfare" in the community has far more to recommend it than the "department of

charities," for one of the great advances made during the last generation has been the recognition that the recipient of relief in any form is entirely within his rights and privileges, and that the donor of such relief, whether government or voluntary, is honor bound to provide it as generously, as gracefully, and as sympathetically as the English language makes possible.

The introduction of the scientific spirit into the practice of medicine, especially into hospital practice where the physician may choose his cases if he is disposed to do so, has brought with it as an undesirable by-product a regrettable lack of interest in those patients vaguely classified as chronic, in whom permanent tissue changes have already taken place and in whom spectacular cures are no longer considered possible. Some of the incurable patients of yesterday are the curable patients of today. It is, therefore, reasonable to expect that some of the incurable patients of today will be the curable patients of tomorrow. The use of the term "incurable" should be condemned as conveying an atmosphere of finality about the patient, as if the social agents had passed a life sentence from which there is no appeal. We would be teaching good medical practice to students of medicine and the social sciences and we would be giving to the investigator an opportunity to study his problem through to a conclusion, if patients could be kept under control from the onset of illness until the complete cure has been achieved beyond reasonable doubt. The scientific and humane care of the patient requires that he be kept under observation until the natural history of his illness has taken its course. The physician who does not seek the line of least resistance and who selects the obscure rather than the obvious in clinical medicine, is at a premium in hospitals.

There is enormous advantage in continuity of care, provided interest in the patient can be sustained. At the present time the sick man who has all the luck is in the acute short-term classification—not too acute, because then he has no choice—has an interesting and tangible condition and meets the requirement of the voluntary hospital on social, economic and clinical grounds. One can almost judge the quality of the acute general hospital by the kind of "clinical material" which it transfers to other institutions such as hospitals for chronic disease, almshouses and convalescent homes. The ability to administer to the needs of a chronic patient successfully is, after all, the acid test of the individual organization that cares for him. "Never say die" is the typical motto of any hospital. It is obviously our duty to keep a hopeless patient alive as long as we can. The hospital which permits curability as an absolute criterion for admission, in an age when differences of opinion on the subject are still sharp, parts company with a fundamental principle of humanity. The criteria of scientific interest, prognosis, curability, age and economic condition should never be established as an instrument of policy by those who are responsible for the maintenance of philanthropic institutions. The process of differentiation whereby contagious and obstetrical cases are separated out and segregated

is easily defended on social grounds, but the desire for specialization based on duration of disease, whereby the chronic groups (loosely termed chronic, incurable and aged) are similarly isolated and often forgotten, can have no defense that has a humanitarian basis. We might note, in passing, that research in chronic disease produces dividends which enable the strong the better to enjoy their strength. "Sweet are the uses of adversity."

The chronic hospital, existing independently of the acute general hospital, is as expensive as it is difficult to maintain. (There is, therefore, only one independent hospital for chronic disease of high standard, in the voluntary classification, of which we have any knowledge.) Some day we shall learn that the true medical center seeks to learn and to teach the natural history of disease in all of its phases, acute, chronic, and "incurable," from infancy to old age, in a group of buildings which separates patients physically for their spiritual well-being, yet gives them, without exception, the most expert medical care available now for only one of these groups.

These random selections reach next to the unfortunate patient who is discharged from the hospital the wrong way. Rightly looked at, every death is a clinical failure. The study of the causes of such failures is the very essence of preventive medicine. Under these circumstances, the hospital is morally obligated to make every reasonable effort in all cases to determine the exact cause of death. This should be a fixed rule, for the additional reason that discoveries in the realm of medicine and surgery are not in proportion to the amount of available clinical material. The progressiveness of a hospital is, indeed, in direct ratio to the laboratory spirit which it maintains.

Clinical failures are extenuated somewhat when those who managed the case seek to bring them to view in order to prevent their repetition. Every patient who goes to his grave with a clinical secret, unstudied, is a reproach to our humanitarian ideals. Hospitals must keep faith with the dead as with the living. There is nothing that will mature an interne more rapidly, nor cause him to think more deeply, than the discussion with the nearest relative of the advisability of post-mortem examination.

Men of science avoid, with great care, the publication of a misleading statement, and do, indeed, retract it, if it was made in good faith and proved to be wrong. Yet there ought to be a rule in scientific medical societies requiring a checkup of all cases reported cured, within a year or so after the claim has been made. No hospital should hasten to claim cures until they have been established in the follow-up clinic beyond reasonable doubt. If the failures in hospitals were reported as often as the successes, and if the successes were checked back from year to year to discover whether time has compelled any changes in conclusions reached at an earlier date, case histories would have greater scientific value. The record room of the hospital is eloquent on this point and does, indeed, contain the mirror of scientific progress in the hospital.

Sir Walter Morley Fletcher, secretary of the British Medical Research Council, once said "Every step forward in medical science is a step toward abolishing surgery." Here is an observation which hospitals would do well to ponder. Several years ago Dr. Libman made the illuminating recommendation that members of the visiting staff be required by a rule of the hospital to sit down for at least one minute at the bedside of every patient during rounds in the ward. Memoranda like these are prominent in my notebook. The tendency to select interesting cases for special attention is understandable, but not to be encouraged by the administration of any hospital. Criticism of hospitalization in America (particularly in large hospitals) has always been aimed at the prevailing method of treating selected patients in wards and neglecting to individualize, which often result in the loss of the most valuable single opportunity to bring the patient back to health and in the failure to win his friendship for the hospital.

The patient is the social entity without whom the hospital would have no reason for existence. The moral obligation of the hospital toward the ward patient is not altered by the fact that he may not bring legal suit against a charitable institution. The social and medical exploitation of the ward (charity) patient is made easy by his poverty and the weakness of his protest. We are, therefore, under a double obligation to avoid it. The poor man hesitates to complain when he gets something for nothing. He does not for the moment see the necessity for progress in medical science and may be permitted an increased degree of selfishness as a protective mechanism in his struggle for life.

In the wards the patient finds himself one of many. He is required to show consideration for sick neighbors, with whom he must share the sympathies and attention of the staff. He naturally craves for the personal interest of someone to replace those who would never have left his side, or relaxed in their solicitude for his welfare, if he had stayed at home. Sickness is a humiliating experience for anyone to endure under any circumstances. When society made the decision that patients, lacking financial means with which to purchase adequate care, could not be treated at home during acute illness with the best results, and considered it in the interest of the sick (and, incidentally, in the doctors' interest) to herd them in wards where they could be treated on a time-saving and efficiency basis, an extraordinarily great risk and responsibility were assumed.

The sick man has the right to ask for the personal interest of the physician to whom he is assigned, without regard to any other consideration than the relief of the condition for which he seeks treatment. The improvement of his habits should not be undertaken during illness, unless these habits interfere with his recovery, or jeopardize the interests of other patients. The mere fact of being sick is not a disgrace, no matter what the sickness may be. To be sick with a disease which could have been prevented with reasonable care is decidedly to the discredit of the patient who

is not the only one to take the consequences, and, one might add, to the community which may not have done its full duty in enlightening him. To continue to suffer from sickness under any circumstances, without seeking the relief which medical men individually and in their organized forms can give is a grave injustice to everyone concerned. Thus the sympathy of the hospital must become aroused and it finds that it has an educational duty to the community.

The patient must always be given the benefit of any doubt. The legal right of selection, retention and discharge of patients, which voluntary hospitals enjoy, often screens a lapse from humanitarianism in the admitting room and in the wards. How long is it since the value of the hospital to the community was measured popularly by its mortality rate? No decent hospital would now think of selecting its patients on the basis of the comparative risk involved. We are reminded here that it is the social service department which bears the burden of the unwanted patient, because it must deal with the consequences when the medical staff or hospital executive puts through a "rush order." It is the social worker who is left holding the bag when the medical men decide that they have exhausted all of their efforts on behalf of the patient.

The patient should not be expected to consent to a major operative procedure until his confidence has been won in the operator and the operation. It is part of the surgeon's duty to convince the patient of the need for such radical treatment and this cannot always be accomplished by labor-saving devices. Even in the mechanical field, labor-saving devices at the bedside of the patient have therapeutic possibilities up to a certain point and therefore have a limited future.

Too often a patient is recorded on discharge as cured when he is cured only of the effects of a surgical operation and not of the disease for which he was operated. The mere relief of signs and symptoms is the more primitive type of cure, while the relief of the underlying condition is a modern achievement. A case should not be stamped cured until it is definitely and finally known to be so from all of the scientific factors at our disposal, including the element of time. The physician might reflect on the thought that time is still the great healer and as dependable as ever.

The identification and treatment of disease is an important, but not an exclusive method of dealing with the problems of the sick man. In the earlier days of the hospital, the knowledge of *materia medica* was sufficient qualification for the practice of medicine, but a finer appreciation of environmental factors in their relation to human infirmities finally showed the importance of discovering and, if possible, correcting social mal-adjustments incidental to disease. People who live in communities where the modern hospital flourishes, pass their lives in a more or less congested environment in which every move of major importance in their lives has its effect on the lives of their neighbors. One of the paradoxes of our

civilized life is the faith that many people have in the extraordinary substances which are used in the treatment of disease (such as chemical compounds of complicated formulae) in contrast to the seeming lack of interest in the routine foodstuffs which are, indeed, taken for granted since they somehow manage to regulate themselves. The psychological explanation for this may be the challenge of the unusual and the mysterious, and the craving for immediate spectacular results from treatment. There is a great deal of waste in public and private expenditure brought about by misleading advertisement and self-seeking practitioners who know the commercial value of a fear complex.

The medical profession has been slow to learn that the treatment of a patient is not always a matter of drugs or surgery, and has paid dearly for its conservatism in the growth of a number of cults which magnify out of all proportion some form of cure which has restricted scientific application. This is, partly, the fault of the hospital, which may not have provided a reasonable amount of experimental equipment for the detection and encouragement of scientific talent. As every hospital administrator knows, physicians and surgeons have selective interests in various kinds of clinical material. This information should be exploited to the best advantage of the patients. No field of medical activity, including dentistry, may safely be neglected, or over-emphasized at the expense of others.

A word of caution should be added as the hospital moves along the progressive road toward perfection. The latter-day attempt to standardize criteria and definitions in a field where practically all clinical situations are unprecedented is a hazardous game from the standpoint of public health and should be undertaken only with the greatest of care and forethought. The problem is how to bring the patient back to health by the best methods known and with the least discomfort to him, while gathering facts concerning his illness which will enable us to improve these methods. No rule of thumb will apply. Every patient is an individual problem.

On final analysis, the hospital administrator after discharging his duty toward his patients, is the servant of the medical staff and must be at its disposal for the advancement of the work of the hospital. Though fortune may favor the physician, the scientific and not the financial yardstick is the measure of his ultimate importance. The administrator, working on a full-time basis, and the scientist working either as a volunteer, full-time or part-time, have a contribution to make on a cooperative basis and neither one can hope for success acting alone.

A NOTE ON THE RELATIONSHIP BETWEEN JAUNDICE IN PIGS AND JAUNDICE IN HUMAN BEINGS

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There are two types of infectious hepatitis (infectious jaundice) which occur in the United States: 1) Spirochetosis icterohemorrhagica or Weil's disease, and 2) a non-spirochetal form.

Weil's disease is rather rare in the United States, the number of proven cases is small, and, so far as I can discover, there have been no epidemics here, such as occurred in Europe during World War I.

Non-spirochetal jaundice has been known here since the early part of the nineteenth century, occurs sporadically as so-called "catarrhal" jaundice, and also occurs in the form of family, institutional and regional outbreaks. At times epidemics are state-wide, as was the case in New York State in 1921 and 1922.

Both forms of infectious hepatitis are probably world-wide in distribution, for although the cause of the non-spirochetal form is unknown, cases clinically resembling this type of the disease have been observed in various parts of the world; the same is true of Weil's Disease.

The purpose of this brief communication is to call attention to the relationship between infected pork and the non-spirochetal type of infectious jaundice, in the belief that this question has not been sufficiently studied in this country.

The histories of two patients will serve as a text:

CASE REPORTS

Case 1. Mrs. A. and her friend Miss X had lunch together January 4, 1935. The luncheon consisted of hot roast pork sandwiches, made with untoasted bread, canned green peas, and tea. On the morning of January 5, Mrs. A. experienced severe pain in the small of the back, so that she had difficulty in turning in bed. She improved under symptomatic treatment and felt well enough January 9 to be out of bed. January 10, after a short automobile ride she became nauseated and vomited, the vomitus being bitter, green mucus. January 11 she was constipated and vomited again. At the next bowel movement it was noted that the feces were grayish and this persisted for several days. Meanwhile the temperature was ranging from 99 to 100.4°F. by mouth, there was loss of appetite, drowsiness, prostration, and jaundice had appeared. Physical examination showed that the skin and mucous membranes were lemon-yellow. The tongue was coated. The abdomen was slightly distended. The liver and spleen were not enlarged, but there was tenderness over the liver, especially in the region of the gall-bladder. The heart and lungs were normal. The urine contained a trace of albumin, yielded a strong test for bile, and, under

the microscope, showed many leucocytes. The fever continued for about ten days, the jaundice gradually faded and had completely gone at the end of two weeks, and recovery ensued.

Case 2. On the morning of January 6, 1935, Miss X, who was just beginning a menstrual period, developed low abdominal pain, felt faint, and vomited. She stayed at home and was seen by her family doctor January 10. At this time she felt miserable, had back and leg aches, and her skin had become distinctly yellow. She had no appetite, and her bowels, always sluggish, were more constipated than usual. She had slight fever, not more than a degree. Her skin was somewhat itchy. Examination showed that the skin was lemon-yellow and the conjunctivae were orange-yellow. The tongue was clean but over-red. The spleen was palpable on deep inspiration. The liver could be felt 4 cm. below the costal margin in the right mid-clavicular line; the edge was tender, especially in the gall-bladder region. The heart and lungs were normal. The urine contained a trace of albumin and was loaded with bile and casts. The leucocyte count varied between 7,600 and 8,800. A differential count showed polymorphonuclear leucocytes, 77 per cent; small mononuclears, 18 per cent; large mononuclears, 3 per cent; eosinophiles, 2 per cent. This patient also recovered after about three weeks of illness.

Here then, were two friends who had taken a meal in common, and each of whom developed, within a day or two after the meal, the clinical picture of infectious hepatitis. There was nothing in the meal which was likely to have caused an infectious process except pork; bread, tea, and canned peas all seemed unlikely sources.

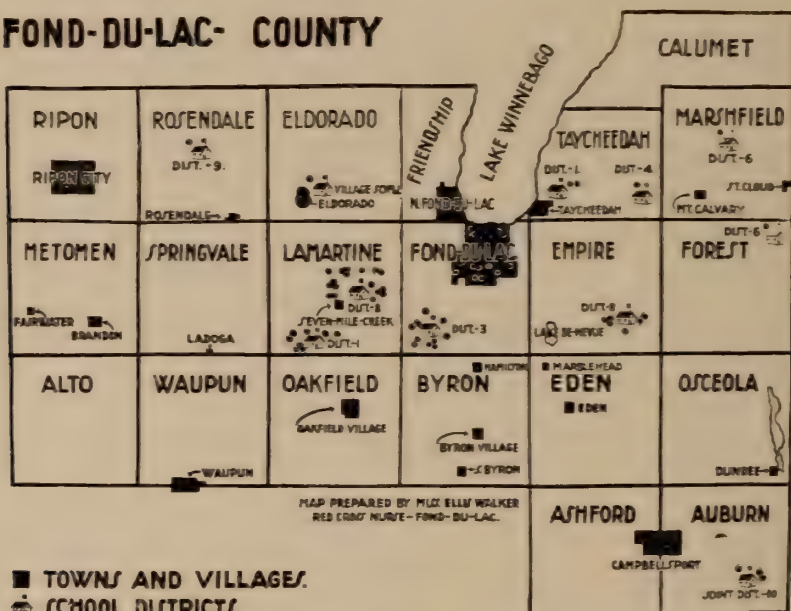
The question of the method of transmission of the non-spirochetal type of infectious hepatitis has been, and still is, the subject of discussion. The three types of transmission which seem possible, in the face of existing evidence, are 1) transmission by contact, either direct or through fomites; 2) droplet infection; and 3) infection through the alimentary tract.

It is difficult, in practice, to clearly separate infection by contact from droplet infection. For example, in the outbreak of infectious jaundice in Fond-du-Lac County, Wisconsin, described in my article of 1923, there was good evidence, obtained by plotting the cases, that the disease was spread by the association of children at country schools. It would be almost impossible to decide in such circumstances, whether infection resulted from direct contact, from fomites, or from droplet infection; all could be possibilities. It is to be noted also that in this epidemic many small towns were completely spared and that the largest town in Fond-du-Lac County had only a few scattered cases. Quite obviously this situation throws doubt on spread by contact or droplet infection only, because, aside from school contact, opportunities for contact in cities are usually greater than they are in the country. If the disease is commonly transmitted by contact or droplet infection, it would be expected that cities, with their buses, street cars, movies, and other places of public congregation, would be more favorable to such spread than country districts. The fact that, in the Fond-du-Lac County outbreak, the disease was more

prevalent in the country and that this could not be explained on the supposition of contact or droplet infection alone, raises the question whether some other method of spread was not present.

One is struck by the resemblance of this situation to that pictured by Andersen in his charts showing that in Denmark, infectious hepatitis is much more prevalent in the country districts than in the cities. Andersen's explanation is that this difference is due to the fact that the inhabitants of the country are much more likely to eat uninspected pork than the inhabitants of the cities. There is no doubt that in this state, and many other American states, a similar situation prevails.

FOND-DU-LAC COUNTY



We may point out that outbreaks of a classical pork-borne disease, trichinosis, are much more likely to occur as a result of the consumption of uninspected pork, home slaughtered in the country, than they are in the cities, where most of the pork has had at least gross inspection, and where sporadic cases are more common.

Credit is due to Thune Andersen (1), of Copenhagen, for calling attention to the relationship between infectious jaundice in hogs and infectious jaundice in human beings. In his first article, published four years ago, Andersen showed that jaundice in hogs was prevalent in Denmark, especially in the country districts; that the presence of this disease did not result in the rejection of flesh from such hogs as food, unless the jaundice was very intense; and that there was a rough correlation between the number of jaundiced pigs sold and the incidence of infectious jaundice in

human beings in different districts. In brief, he presented epidemiological evidence that strongly suggested a relationship between porcine and human infectious hepatitis.

In a second article covering animal experiments with hepatitis, published by Andersen and Tulinius (2), it was shown that human infectious hepatitis could be transmitted to pigs, and that the infection could then be passed from these to other pigs. It was shown also, that the pathological lesions of human and porcine hepatitis were identical.

The cause of the condition was not discovered, and one may suspect that it is probably a filterable virus. Supporting this view is the known fact that immunization of human beings by attenuated viruses, notably that of yellow fever, is not infrequently followed by infectious jaundice. However, it is still a question whether this may not be purely coincidental.

In view of my experience with the two patients reported in this paper I took up with the State Health Department, and also with the Department of Agriculture in Washington, the question of jaundice in pigs in the United States. I found that the disease was not officially recognized but that there was little doubt that it occurred. The Department of Agriculture, in fact, called my attention to the report of an epidemic in Iowa. However, it was obvious that no special attention had been focussed on the infectious hepatitis of pigs as a possible source of human disease. In correspondence with Dr. Thune Andersen I found that an exactly similar situation had existed in Denmark. In a letter written me in 1938 he says: "You too said, that the authorities did not know anything about porcine hepatitis. It was just the same case here in Denmark, and I had great trouble to get the exact numbers of the infected pigs here."

In conclusion, I would state that it is not my purpose to claim that the non-spirochetal type of infectious hepatitis is always due to the consumption of pork from jaundiced pigs. It is quite possible that the disease may be transmitted in various ways, including droplet infection and contact. The point I wish to emphasize is, that the possibility of transmission of infectious hepatitis from pig to man has not been sufficiently considered in this country, and that this question, as well as the more general one of the prevalence of infectious jaundice in American pigs, needs further investigation.

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ANGINA PECTORIS AND THE PEPTIC ULCER SYNDROME

PRELIMINARY REPORT

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Although statistical studies do not reveal an unusually high incidence of peptic ulcer in patients with coronary artery sclerosis (1), these two conditions manifest many striking relationships, which may give rise to several clinical patterns. Most dramatic are cases in which acute recurrent symptoms of peptic ulcer, and the simultaneous onset of symptoms of angina pectoris are ushered in by an attack of severe epigastric pain, accompanied by electrocardiographic changes typical of acute myocardial damage.

CASE REPORTS

Case 1. History. A. G., a man, was first seen at the age of 60 complaining of dizziness, intensified by bending or twisting the head. At the age of 42 he had had an operation for peptic ulcer and had experienced no subsequent symptoms. Examination revealed slight enlargement of the left ventricle, and a blood pressure of 190 systolic and 90 diastolic. The electrocardiogram showed the QRS slurred in all leads, and measuring 0.12 second. Thereafter he was confined to the house most of the time because of weakness, particularly manifested in the legs on walking. About nine months later he was awakened one night by an attack of severe epigastric pain which lasted three hours, and which was associated with spasm of the upper abdomen. Following this attack his weakness increased, and six weeks later he began to complain of left upper parasternal and epigastric pain occurring two hours after meals, and awakening him at 2 A.M. The pain was relieved by food and by alkali. During this same period he experienced similar left chest and epigastric pain on walking, compelling him to slow his pace. This pain on effort occurred at any hour of the day.

Examination three months after the severe nocturnal attack showed no change in the cardiac findings. However, the T wave had become low and diphasic in lead I and negative in lead IV. These findings evidenced progressive myocardial damage. There was no abdominal tenderness.

Comment. In this case a prolonged severe attack of nocturnal epigastric pain was followed by recurrence of symptoms of peptic ulcer, and the development of symptoms of angina pectoris. These were followed by changes in the electrocardiogram indicative of myocardial damage. Does this sequence represent a coronary closure with epigastric localization of pain, or simultaneous vascular damage in the gastroduodenal and the coronary arteries? We have described a similar case in which roentgen and electrocardiographic studies revealed simultaneous cardiac infarction and peptic ulcer (2).

In other cases, with long standing ulcer symptoms, the acute onset or recurrence of anginal pain has the post-prandial timing of peptic ulcer.

This is particularly striking in patients with gradual closure of a coronary artery, or so-called prodromal symptoms of coronary thrombosis, in whom anginal attacks at rest occur repeatedly one to two hours after meals, and are, therefore, erroneously interpreted as being caused by peptic ulcer.

Case 2. History. I. M., a man, aged 60. At the age of 45 he first noted mid-sternal heartburn occurring one to three hours after meals, and relieved by taking alkali. Occasionally he would be awakened at 2 A.M. by this pain. Remissions of the pain lasting from one to two weeks occurred from time to time. At the age of 53 he suffered a left renal colic and subsequently passed a stone. At the age of 55 he first noted that walking a few blocks provoked mid-substernal pressure radiating to the throat, the upper dorsal spine, and at times to the left arm, compelling him to rest, with relief. At the age of 57 he was awakened one night by mid-substernal pressure radiating as before to the throat and left arm, lasting one hour, and relieved by morphine taken by mouth. About a week later attacks of mid-substernal pressure, lasting as long as an hour, recurred from time to time, always two to three hours after meals. Several times he was awakened at about 2 A.M. by similar pressure under the sternum. Although the episodes of substernal pressure occurred two to three hours after meals like his original heartburn, he distinguished very carefully between them and the old heartburn.

Examination. The general physical examination revealed no abnormalities. Fluoroscopy revealed a heart of normal size and configuration. The heart sounds were of good quality and there were no murmurs. Blood pressure was 130 systolic and 90 diastolic. The electrocardiogram showed low voltage of the T waves, particularly pronounced in lead I. The S-T interval was depressed in leads I and IV.

Course: He was put to bed for two weeks. One week later, after returning to work, he suffered a particularly severe attack of mid-chest pressure lasting two hours. A hypodermic injection was administered and he remained in a hospital for four weeks. Thereafter he noted greater difficulty in walking. At best he could walk about one or two blocks, when he would experience the substernal pain compelling him to rest for a few minutes. From time to time the old mid-substernal heartburn recurred two hours after meals, but there was no relationship between the coronary and ulcer-like pain. Re-examination two and a half years later showed little change. The T wave in lead I had become flat and the S-T depression in lead IV was no longer present.

Comment. This case history illustrates the ulcer-like timing of repeated anginal attacks which ultimately end in a coronary thrombosis. This post-prandial "peptic" timing of anginal pain suggests that whatever factors may be operative in inducing ulcer pain may at the same time be direct or indirect determinants of anginal pain. The mechanism of peptic ulcer pain is not clear. When it is more precisely understood, factors underlying anginal pain may at the same time be unearthed. It is likely that this will take us into metabolic fields, into the relationship of meals to acidity changes and blood sugar fluctuations.

The intimate relationship between the syndromes of angina pectoris and peptic ulcer, and the close correlation in the activity of symptoms of both conditions is exemplified in patients in whom tolerance for walking increases coincident with effective treatment of peptic ulcer-like symptoms. During periods of peptic ulcer pain, which often last for several weeks at a time, the pain of angina pectoris is induced more readily and on slighter provocation. As the peptic ulcer symptoms are brought under control

by diet and medication, the anginal pain either is provoked less readily or remits entirely. Paradoxically these patients can often walk more easily shortly after meals, with the stomach full. In the usual patient with angina pectoris it is the rule that anginal pain on effort is induced most readily shortly after the ingestion of food, when the stomach is full.

The following case illustrates greater ease in walking shortly after meals.

Case 3. History. A man, aged 54. For over 20 years he suffered from lower sub-sternal heartburn, occurring one to two hours after meals, and relieved by alkali. The pain would remit for several years at a time. No gastro-intestinal x-rays were taken. At the age of 50, several hours after breakfast, and while being shaved he experienced a sudden attack of palpitation associated with very slight midsternal pain. There was no breathlessness. Examination one hour later revealed regular sinus rhythm, the heart rate was 80 beats per minute; blood pressure 138 systolic and 90 diastolic; the heart sounds were dull; there were no murmurs. The electrocardiogram taken on the following day showed a PR interval measuring 0.22 second and moderate lowering of the T waves in all leads. During the next four years he continued at his work and felt quite well, and was able to walk freely at all times. At the age of 54 he first began to experience left lower chest and lower substernal pain, occurring intermittently, but chiefly three to four hours after meals, and relieved by food. One week after the onset of these symptoms, while walking, he experienced epigastric pain radiating to the lower chest and compelling him to rest. He was then given a Sippy diet with powders. Epigastric pain on walking continued for three weeks, when weakness and very slight lower mid-chest pain replaced the epigastric pain on walking. The chest pain would be relieved by a short rest. During this time he noted that he could walk more freely and greater distances on a full stomach. After being on the diet for five weeks all symptoms remitted and he was re-examined two weeks later. At this time the general physical examination was unchanged, but the electrocardiogram now exhibited normal voltage of the T waves in leads I and II.

Comment. This case history, in addition to pointing out the increased capacity for walking after meals, illustrates the clinical appearance of previously silent coronary artery disease, simultaneously with recurrence of peptic ulcer symptoms. It shows too the remission of the anginal syndrome, coincident with the relief of the peptic ulcer pain by medication and diet.

Anginal pain that is experienced in the abdomen, or that radiates to the abdomen suggests that the patient has had previous ulcer symptoms. The abdominal localization of the pain may be conditioned by sensitization of the corresponding nervous pathways by the antecedent peptic ulcer.

Case 4. History. A man, aged 54. At the age of 40, for a period of five months, he had suffered upper abdominal pain immediately after meals, lasting five to ten minutes, and intensified by food. Roentgenographic study is said to have shown a peptic ulcer. The symptoms remitted shortly after a diet was prescribed. At the age of 45, when in apparently good health, while walking he suddenly experienced dizziness, spots before the eyes, and sticking pain in the lower left chest, radiating down the left arm to the fingers, which felt numb. The pain lasted about one hour. He was bedridden for about ten weeks. Then he returned to work and again enjoyed good health except that climbing stairs now provoked pain in the upper abdomen, compelling him to rest. At the age of 47 he was awakened at 2 A.M. by pain in the

left chest that radiated first to the epigastrium and then to the left subcostal area, and lasted about a half an hour until he received a hypodermic injection. He then enjoyed good health until the age of 50, when he suffered, within the space of two weeks, repeated attacks of left hypochondriac pain radiating to the throat as a choking sensation and lasting one-half hour. For this he was kept in bed some twelve weeks and thereafter could walk but half a block when epigastric pain would set in and compel him to halt. His work as a tailor involved the use of his right arm particularly, and during abduction movements he would experience sticking pain about the apex and with this is a pressure pain in the epigastrium. If he continued at his work, dizziness would set in and finally he would be compelled to rest.

Examination. At the age of 50, four months following the repeated spontaneous attacks, the examination disclosed no abdominal tenderness. Fluoroscopy revealed a heart of normal size and configuration. The heart sounds were of good quality, there were no murmurs; the blood pressure was 120 systolic and 85 diastolic. The electrocardiogram showed very prominent Q waves in leads II and III. The T wave in lead II was shallow and diphasic and in lead III the T wave was deep and inverted.

Comment. The case illustrates so called "abdominal" angina. In such cases one should suspect the presence, or the past existence of a peptic ulcer. At the moment a gastro-intestinal x-ray may show no ulcer, but the abdominal pattern of the angina is conditioned by the old ulcer. It is known that anginal pain may radiate to or arise in areas distant from the heart, whose nervous pathways have been sensitized by previous local disease; e.g. shoulder, spine, gall bladder, abscessed tooth (2).

DISCUSSION

Initial symptoms of peptic ulcer are manifested at a much earlier age than those of angina pectoris. The simultaneous onset of the two diseases is rare, although their simultaneous occurrence is common. Even the taking of a most careful history often fails to elicit the old history of symptoms characteristic of peptic ulcer, for they may be so mild they are often overlooked and forgotten, especially after the lapse of several decades. Indeed in not a few instances, when old ulcer symptoms are suspected because of the nature of the anginal symptoms, a history of ulcer pain is elicited only after further questioning. It is imperative to unearth these old symptoms if diagnosis and treatment are to be correct.

These observations throw some light on so-called abdominal angina, in which abdominal pain occurs on effort and in the course of an acute attack of coronary thrombosis. The cross radiation of anginal and peptic pain when both diseases co-exist has been discussed in a previous communication (2). With the appearance of coronary disease, ulcer pain formerly experienced solely in the upper abdomen, may radiate to the chest and even to the upper extremities. Further when the pain of coronary disease occurs in a patient with previous peptic ulcer, it may radiate to or originate in, the upper abdomen.

SUMMARY

We have presented cases to illustrate the intimate relationship that may be manifested between the symptoms of angina pectoris and peptic ulcer.

1. There may be a sudden simultaneous onset of ulcer symptoms and of anginal symptoms.
2. Repeated attacks of angina pectoris at rest ending in coronary thrombosis may occur two to three hours after meals and during the night at the characteristic "ulcer hours."
3. When symptoms of angina pectoris and peptic ulcer co-exist, successful treatment of the ulcer symptoms may cause remission of the anginal syndrome.
4. Epigastric localization of anginal pain may be conditioned by a pre-existing peptic ulcer.

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THE KIDNEYS IN SUBACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS¹

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With almost no exceptions the kidneys during the course of subacute streptococcus viridans endocarditis develop lesions. However, only a few of these patients develop lesions extensive enough, or of a nature, to produce during life evidence of marked renal insufficiency; some patients even continue to excrete a normal urine in normal amount, when post-mortem observation reveals the existence of definite, sometimes quite marked, renal lesions.

At the Peter Bent Brigham Hospital I have studied clinically and pathologically 61 cases of subacute endocarditis caused by *Streptococcus viridans*. The gross changes in the kidneys are those described in the autopsy protocols of the Department of Pathology of the Peter Bent Brigham Hospital; the slides used for microscopic study come from the slide cabinet of the same Department; for this data and for the use of the slides I record my thanks.

First I will describe the pathological lesions observed in the kidneys of these 61 patients. In macroscopic appearance the kidneys of subacute streptococcus viridans endocarditis show three main departures from normal; 1) slight swelling and edema, 2) areas of infarction usually of the anemic variety and 3) focal hemorrhages, which, as they show on the surface of the kidney, cause the appearance, which has been well named the "flea bitten" kidney, a term according to Horder (1), which had been popularized by use in the laboratory of Guy's Hospital, London.

Renal infarction was observed in 56 (91.8 per cent) of the 61 patients. In 42 of these the infarct was noted in the gross description of the kidney, while in 14 it was observed only under the microscope in an examination of the available slides. It is obvious that infarcts can be overlooked in the gross inspection of the kidney; this is to be expected, if the infarct is of recent origin and occurs in a rather pale kidney. Then it becomes a matter of chance whether the block of kidney, saved for histological study, contains an infarcted area or not. The total number of infarcts discovered in these kidneys probably is less, rather than more, than actually occurred. If there had been no microscopic study of the kidney, the percentage of

¹ This study was aided by a grant from the Milton Fund of Harvard University given to study the accumulated clinical records of the Medical Service of the Peter Bent Brigham Hospital in Boston.

infarcts would have been reduced from 91.8 per cent to 68.85 per cent. This needs to be kept in mind in regard to the frequency of renal infarction reported by others in subacute streptococcus viridans endocarditis.

In my series of 61 cases 8 (13.11 per cent) showed surface focal hemorrhages to constitute "flea bitten" kidneys. This is a lesser frequency than would be expected from statements often made concerning the pathological appearance of the kidney in subacute bacterial endocarditis (Libman and Friedberg (2)).

In the microscopic study of the kidneys from these cases of subacute streptococcus viridans endocarditis a variety of glomerular lesions, both diffuse and focal in distribution, have been observed. The most frequent glomerular lesion is proliferation of the cells of the capillary loops (figs. 1 and 2); the intracapillary endothelial cells are the ones usually showing proliferation most extensively, although the pericapillary epithelial cells show some increase in number in this lesion. Bell (3) calls this lesion, along with the one next to be described, acute glomerulitis. This proliferative glomerular lesion is a lesion diffuse in its distribution in sections of the kidney, although not necessarily every glomerular tuft shows cellular proliferation. In individual glomeruli the capillary tuft usually is involved pretty uniformly, giving it a cellular, solid appearance with the lumen of the capillary loops not visible (figs. 1 and 2); however, in some kidneys only a portion of the glomerular tuft shows cell proliferation, while most of the tuft is normal, sometimes with capillaries filled with blood (fig. 3). The degree of cell proliferation varies in different kidneys from very slight to very marked.

In some of the glomeruli groups of cells in the glomerular tuft are granular, their nuclei stain poorly, and individual cells cannot be distinguished but seem fused together (fig. 4); in others degeneration is more marked, nuclei disappear, and leucocytes make their appearance both in the capillaries of the tuft and in the tissue about the glomerulus (fig. 5); this may involve the glomerular tuft quite generally (fig. 5) or only in part (fig. 6); in some glomeruli fibrin threads appear between groups of degenerated cells (fig. 7). As will be described later on, these areas of cell degeneration in the glomerular tufts may lead to thrombosis of a capillary loop and so become a cause of a focal glomerular lesion.

This type of glomerular lesion definitely is not a focal lesion, and it is not to be explained on the basis of a thrombotic or embolic process; it is a diffuse process analogous to that seen in the ordinary type of acute intracapillary glomerulo-nephritis; it seems reasonable to consider it of toxic or allergic origin. This cellular, proliferative, glomerular lesion was seen in 48 (80.32 per cent) of the 61 cases of subacute streptococcus viridans endocarditis studied by me.

Another diffusely scattered glomerular lesion is thickening of the basement membrane of the capillaries of the glomerular tuft (figs. 8 and 9).

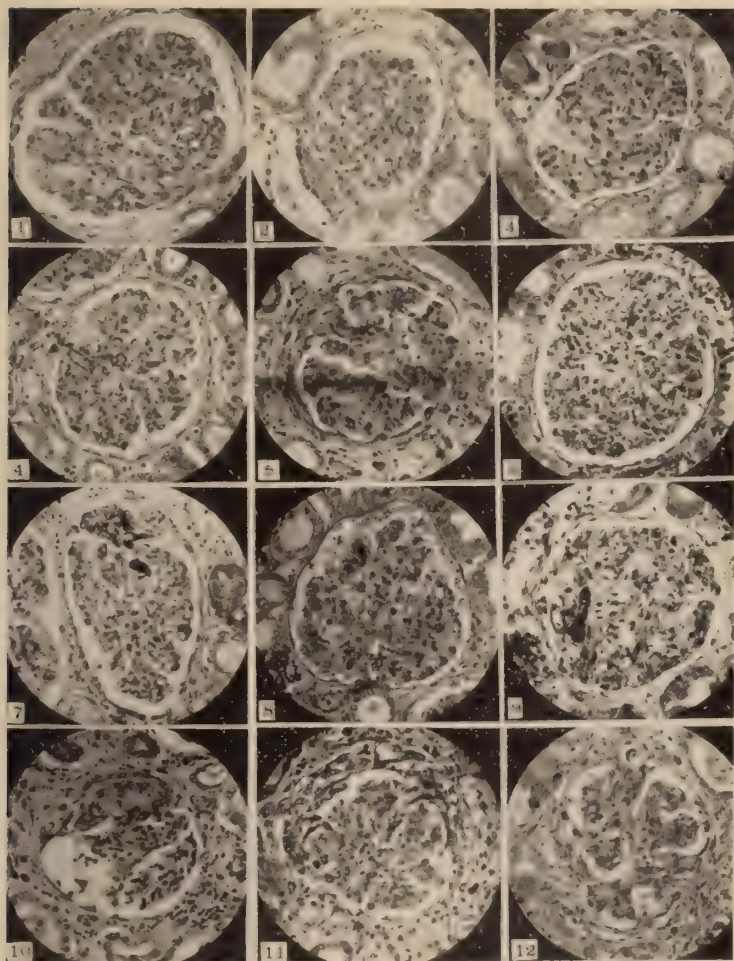


FIG. 1. Proliferation of cells of glomerular tuft. Note lack of blood; cell degeneration in several loops; $\times 360$.

FIG. 2. Proliferation of cells of glomerular tuft and degeneration of epithelium of tubules; $\times 360$.

FIG. 3. Engorged capillary loops except one group with cell proliferation: degeneration of epithelium of tubules; $\times 360$.

FIG. 4. Proliferation of cells of glomerular tuft with groups showing degeneration; degeneration of epithelium of tubules; $\times 360$.

FIG. 5. Degeneration of proliferated cells of tuft with leucocytic invasion and proliferation of epithelium of capsule; $\times 360$.

FIG. 6. Glomerular tuft with cell proliferation of half and cell degeneration with leucocytic infiltration of half; $\times 360$.

FIG. 7. Proliferation of cells of glomerular tuft with degeneration and fibrin deposition in one part; $\times 360$.

FIG. 8. Proliferation of cells of glomerular tuft and hyaline thickening of capillary wall; two degenerated cells with large, pyknotic nucleus; $\times 306$.

FIG. 9. Hyaline thickening of wall of blood vessel; one fibrinoid thrombus; $\times 360$.

FIG. 10. Epithelial crescent; moderate proliferation of cells of glomerular tuft; $\times 360$.

FIG. 11. Like Fig. 10; epithelial crescent larger, with syncytial formation at one point; $\times 360$.

FIG. 12. Similar to Fig. 11; $\times 360$

This was noted in 10 kidneys (16.39 per cent). Since no special stains to demonstrate connective tissue fibrils were applied, this lesion probably was not seen as often as it actually occurred, particularly in the very cellular glomeruli; it stands out more clearly in glomeruli with no, or only slight, proliferation of the cells of the capillary loops. Of the 10 cases, in 4 no cell proliferation was seen; these added to the 48 cases with cell proliferation already noted increases the number of kidneys showing diffusely scattered, glomerular lesions to 52 or 85.24 per cent of the total number of kidneys studied in this series.

In addition to the two types of diffuse glomerular lesions, just described, a variety of focal glomerular lesions were seen in these kidneys. These are of five varieties; 1) proliferation of the capsular epithelium, so-called epithelial crescents, in 36.06 per cent of the kidneys, 2) focal fibrous lesions, chiefly projecting from the capsule into the capsular space of the glomerulus, sometimes within the glomerular tuft, seen in 26.23 per cent of the kidneys, 3) complete disorganization of the glomerulus, an occasional lesion, 4) hyaline, fibrinoid thrombi in blood vessels of the glomerulus, noted in 40.98 per cent of the kidneys, 5) masses of bacteria in glomerular blood vessels, observed in 6.55 per cent of the kidneys.

All of these focal glomerular lesions varied in frequency in sections from different kidneys; in any given kidney different types of focal lesions might be found; more than one might appear in a single glomerulus; only rarely did focal lesions dominate the histological appearance of a kidney. With few exceptions these focal lesions occurred in glomeruli showing diffuse lesions, either proliferative, cellular lesions or thickening of capillary wall; for example both the epithelial crescents and the hyaline, fibrinoid, thrombotic lesions were seen only twice in kidneys devoid of diffuse glomerular lesion. Some observers, notably Baehr (4), have stated that the focal glomerular lesions of subacute bacterial endocarditis usually were found in glomeruli otherwise of normal appearance; others, as Bell (3), fail to agree to this. My own findings are in agreement with the latter finding.

Proliferation of the epithelium of Bowman's capsule to form epithelial crescents is shown in figures 5, 10 to 28 and 40 to 42. As seen in these various figures, there may be only a small group of proliferated epithelial cells or a large group almost surrounding the glomerular tuft or replacing or compressing a varying proportion of it with varying intermediate extent of lesion. In some sections a glomerulus will show only cells apparently of this derivation with no remains of capillary tuft. At first these cells, when few in number, are rectangular or cuboidal in shape and then become increasingly spindle-shaped with spindle-shaped nuclei (see figs. 5 and 10 to 28). Some cells become multinuclear and in places seem to form a syncytium (figs. 10, 16, 17 and 28). The cells forming the crescent often degenerate in places, the cytoplasm becoming granular and the nuclei pyknotic and disappearing (figs. 10, 13, 25 and 27) and fibrin threads (figs. 11, 17, 25 and 28) or red blood cells (figs. 23, 24 and 26) appear among

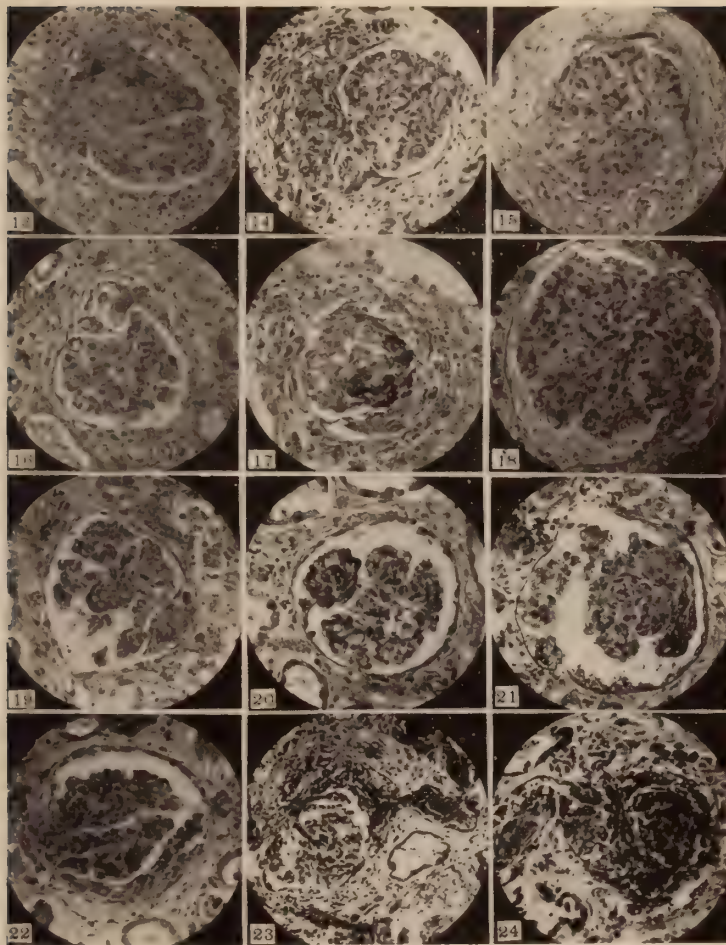


FIG. 13. Epithelial crescent with fusion to both capsule and tuft; glomerular tuft, cellular, occupying $\frac{1}{4}$ of glomerulus; $\times 360$.

FIG. 14. Loose textured epithelial crescent partly surrounding somewhat cellular tuft; $\times 360$.

FIG. 15. Epithelial crescent showing fibrous tissue fibrils occupies over $\frac{1}{2}$ of glomerulus, continuous with capsule and tuft; $\times 360$.

FIG. 16. Loose textured, syncytial type of epithelial crescent; $\times 360$.

FIG. 17. Fibrin deposit among degenerated proliferated cells of both tuft and epithelial crescent; $\times 360$.

FIG. 18. Proliferation of cells of glomerular tuft with small epithelial crescent at point of contact of former with capsule; $\times 360$.

FIG. 19. Similar to Fig. 18 with syncytial formation; $\times 360$.

FIG. 20. Rounded mass of proliferated epithelial cells connected to capsule by a few cells; $\times 360$.

FIG. 21. Similar to Fig. 20 with proliferated epithelial cells continuous with proliferated cells of tuft; $\times 360$.

FIG. 22. Epithelial crescent lining nearly half of capsule; $\times 360$.

FIG. 23. Spindle-shaped, proliferated cell, epithelial crescent, extending from glomerulus into efferent tubule; $\times 260$.

FIG. 24. Similar to Fig. 23: cells degenerated with hemorrhage at one point; $\times 360$.

them or separate the proliferated capsular epithelium from the glomerular tuft (figs. 17 and 28). Such masses of fibrin (figs. 30 and 31) or blood (fig. 29) sometimes are seen in glomerular spaces in which no proliferation of the capsular epithelium is observed.

In a few places the efferent tubule is seen to be filled with spindle-shaped cells continuous with those about the glomerular tuft (figs. 23, 24 and 26) as if proliferated, spindle-shaped, epithelial cells have been protruded from the glomerular space into the tubule, now lined by flattened cells, or as if cells derived from the tubule have proliferated and undergone a spindle-shape transformation and then grown into the capsular space.

The focal lesions just described, epithelial crescents, may have developed in any one of several ways. In some glomeruli the glomerular tuft adjacent to the cells proliferated from the epithelial covering of the capsule looks just like those of the rest of the tuft (figs. 10, 11, 12, 22 and 25); what has caused focal proliferation of this epithelium seemingly is the same as the cause of the cell proliferation in the capillaries of the tuft and suggests a toxic or allergic response. In places there is the suggestion that the cells of a portion of the capillary loop near Bowman's capsule have degenerated (figs. 11, 13, 18, 19, 25 and 27), possibly even a thrombus has formed in the capillary loop, and this process has stimulated the capsular epithelium to proliferate, or at this point some toxic substance has escaped and stimulated cell proliferation. In other places (figs. 20, 21 and 19) it looks as if epithelial cells of the capsule, reflected over the glomerular tuft, have proliferated to surround and gradually replace a degenerated cell group of the tuft or a thrombosed capillary loop and then become attached to the capsule without or with proliferation of the cells lining the latter; in some glomeruli (fig. 13) these two components seem indistinguishably fused together. These explanations have a basis in the fact that lesions of this type may develop when uranium nitrate is given to rabbits subcutaneously or intravenously (5, 6) and in larger number, if the uranium is injected into one renal artery.² These experiments show that bacteria or emboli are not necessary to the formation of this type of focal glomerular lesion. On the other hand they can be produced experimentally (7) by an intracardiac suspension of streptococci and agar. On the basis of this work, the conclusion is not justified that the primary cause is bacterial, the bacteria initiating an embolic-thrombotic process as was thought by Baehr (4) and by Löhlein (8); such an explanation, however, may not be correct.

² It is interesting that in the paper of Christian and O'Hare (5) in 1913 in description or illustration will be seen all of the glomerular lesions, both diffuse and focal, which have been demonstrated in the present paper except the fibrous focal lesion, described in the next paragraph, and, of course except the masses of cocci. In other words, subcutaneous or intravenous injection of uranium nitrate into rabbits was shown to cause glomerular lesions of the type seen in man dead of subacute streptococcus viridans endocarditis.

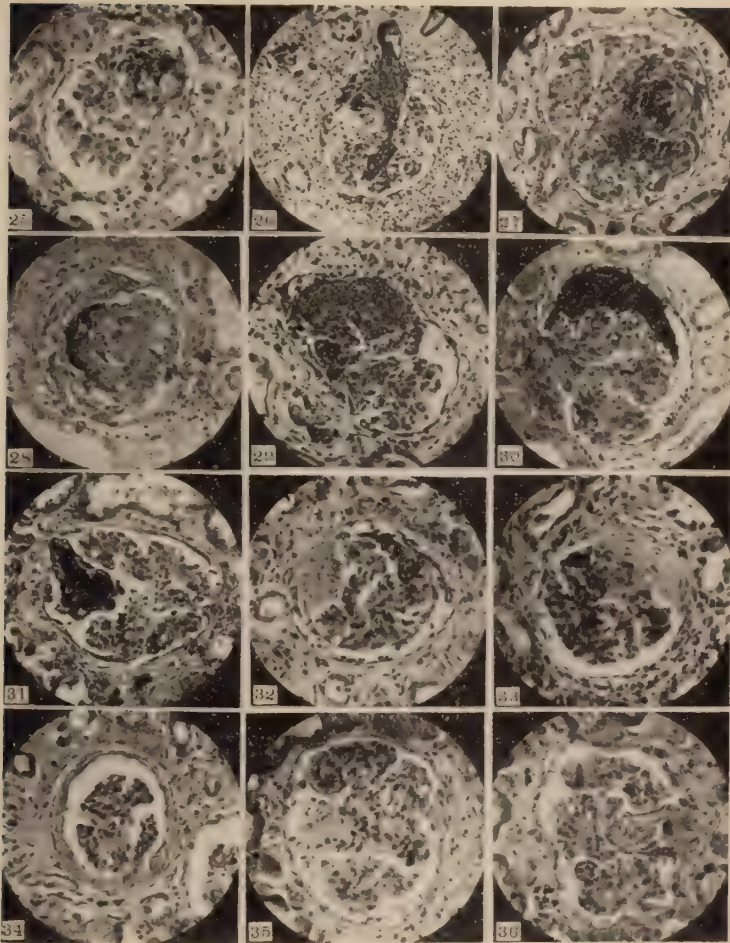


FIG. 25. Glomerulus made up $\frac{3}{4}$ of cellular tuft and $\frac{1}{4}$ of proliferated epithelial cells, the latter interposed with fibrin masses; $\times 360$.

FIG. 26. Glomerulus contains elongated mass of fibrin and blood extending into efferent tubule; at one side a flattened mass of epithelial cells; $\times 260$.

FIG. 27. Glomerulus with large mass of degenerated cells and fibrin; $\times 360$

FIG. 28. Large epithelial crescent half surrounding cellular tuft with fibrin mass between them; $\times 360$.

FIG. 29. Large hemorrhage with degenerated epithelial cells at side of cellular glomerular tuft; $\times 360$.

FIG. 30. Large fibrin mass in capsular space at side of cellular glomerular tuft; $\times 360$.

FIG. 31. Similar to fig. 30; $\times 360$

FIG. 32. Small, hyaline, fibrous mass projecting into capsular space; glomerular tuft cellular; $\times 360$.

FIG. 33. Similar to Fig. 32; fibrous mass larger; $\times 360$

FIG. 34. Hyaline fibrous tissue almost surrounds cellular glomerular tuft; $\times 360$

FIG. 35. Hyaline, fibrous mass within cellular glomerular tuft; $\times 360$

FIG. 36. More cellular fibrous mass covered by flattened epithelial cells projecting from capsule into glomerular tuft; $\times 360$.

Another focal lesion (figs. 32 to 38), a fibrous lesion, is very similar to the epithelial crescent type of focal lesion in distribution both in the kidney section and in the glomerulus; it may vary in size; it may occupy one side of the glomerular space projecting from the capsule; rarely it surrounds the glomerular tuft (fig. 34); it may not touch the tuft, or it may be fused with it (figs. 33 and 38); it may lie within the tuft without impinging on the capsule of the glomerulus (fig. 35). Often it is covered in part or entirely by a layer of swollen, flat or cuboidal, epithelial cells derived from Bowman's layer (fig. 36). In an occasional kidney a similar fibrous change has taken place almost throughout the structure of the glomerulus (figs. 40 and 47). This lesion is cell-poor and fibrillar; often it has an hyaline appearance. With 3 exceptions these fibrous lesions were in kidneys showing epithelial crescents in other glomeruli; in all but one kidney cellular proliferation in the glomerular tuft was present also.

There is the suggestion that these fibrous excrescences from Bowman's capsule represent an older stage of the epithelial crescents and that the latter show transitions to the fibrous stage. With the kidneys showing the fibrous lesions, the duration of illness has been in only one case as short as 2 months, in 3 cases 3 months and in the others from $3\frac{1}{2}$ to 9 months. The shortest duration of illness in cases, whose kidneys show epithelial crescents, was 6 weeks in one case and 2 months in 5 cases; in all others duration of illness was longer. In contrast, the diffuse glomerular lesion with cell proliferation may be present after a shorter period of illness, in 15 cases after 6 weeks of illness or less, in 5 cases after 6 weeks of illness, in 3 cases after 5 weeks, in 3 cases after 4 weeks, in 2 cases after 3 weeks and in 2 cases after $2\frac{1}{2}$ weeks of illness. On the other hand duration of illness by no means determines the frequency and degree of diffuse glomerular lesions nor the frequency and character of focal glomerular lesions. In fact, except in a very general way, duration of illness has very little relation to what lesions the kidneys show.

In a few cases some glomerular lesions have progressed to a stage of complete disorganization of glomerular structure. This change seems to have come about in a variety of ways. In some glomeruli proliferated cells, resembling epithelial more than endothelial cells, have multiplied and gradually replaced the capillary loops of the glomerular tuft (figs. 39 and 43), sometimes seemingly crowding out the capillary loops partially or completely (figs. 40, 41 and 42). In other glomeruli it looks as if epithelial cells have become spindle shaped and separated by connective tissue strands until finally a cell poor connective tissue comes to occupy the place of the glomerular tuft and is partly or completely fused to the capsule, sometimes leaving spaces lined by flattened or cuboidal cells, probably derived from the epithelial cells formerly lining Bowman's capsule (figs. 40, 41, 42, 45 and 46). In still other glomeruli there is the appearance as if the blood flow to the glomerulus has been obstructed with consequent

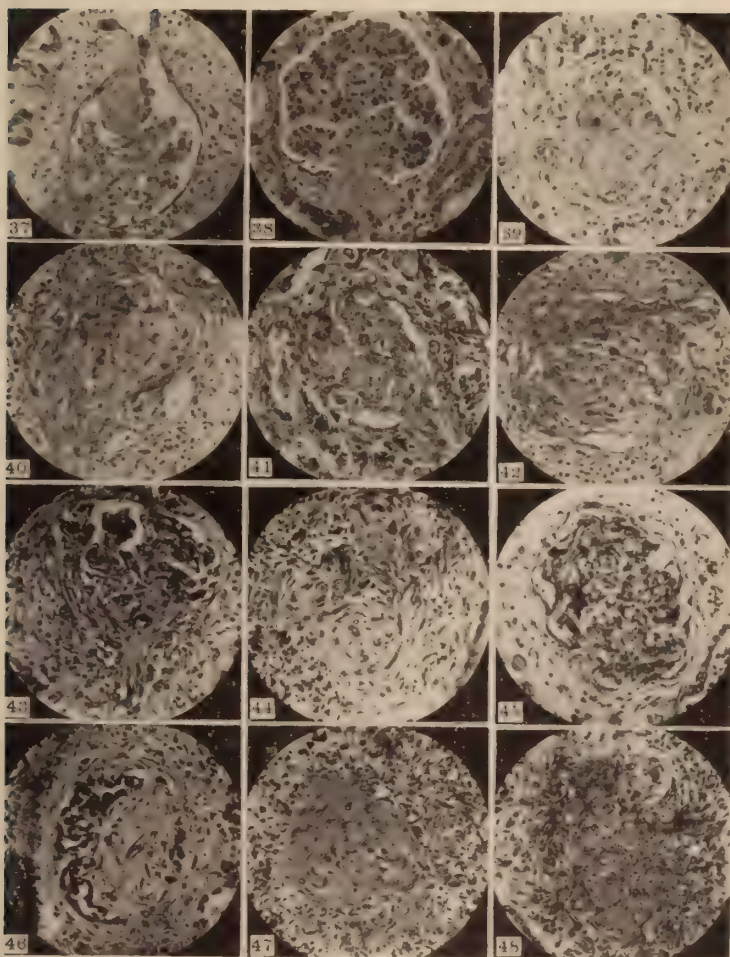


FIG. 37. Similar to Fig. 36; fibrous mass less cellular; $\times 360$

FIG. 38. Fibrous tissue mass forming a pedicle to moderately cellular glomerular tuft; $\times 360$.

FIG. 39. Usual glomerular structure $\frac{3}{4}$ replaced by cellular fibrous mass probably having begun as epithelial crescent; $\times 360$.

FIG. 40. Tissue as in Fig. 39 has replaced glomerular tuft leaving few spaces lined by flattened epithelium; $\times 360$.

FIG. 41. Similar to Fig. 40; $\times 360$

FIG. 42. Similar to Fig. 40 but in part more resembling structure of epithelial crescent; $\times 360$.

FIG. 43. Glomerular structure $\frac{3}{4}$ replaced by mass of fairly cellular, fibrous tissue; $\times 360$

FIG. 44. Glomerulus replaced by cellular fibrous tissue, in one part showing necrosis; $\times 360$.

FIG. 45. Glomerulus composed $\frac{1}{2}$ and $\frac{1}{2}$ of fused cellular glomerular tuft and epithelial crescent of cellular fibrous type; at periphery small spaces lined by flattened epithelium; $\times 360$.

FIG. 46. Glomerulus replaced by cell-poor fibrous tissue and degenerated flattened epithelium about small irregular spaces; $\times 360$.

FIG. 47. Glomerulus represented by rounded, moderately cellular, fibrous tissue surrounded by loose cellular tissue infiltrated with leucocytes; $\times 360$.

FIG. 48. Similar to Fig. 47 but with extensive necrosis; $\times 360$

swelling of the tuft, degeneration and necrosis of the cells, deposition of fibrin and periglomerular infiltration with leucocytes (fig. 49). In some glomeruli hyaline fibrous tissue forms, and a rounded mass of this is all that remains of the glomerulus (figs. 44 and 47). It would seem also that young connective tissue may grow into the remains of glomeruli, and this intermixed with glomerular remnants and leucocytes has little semblance to the original glomerulus (figs. 44 and 48). As might be imagined, a large variety of structures result to represent partially or completely disorganized glomeruli. Often in the surrounding cellular connective tissue there are many infiltrating polymorphonuclear leucocytes (figs. 47 and 48). Here and there in other cases leucocytes are seen invading disorganized glomerular tufts (fig. 51). In some glomeruli necrosis is seen (figs. 44 and 48). Nowhere except in some infarcted areas has leucocyte invasion reached a degree to constitute miliary abscesses, and this even is a very infrequent happening in the infarcts of our 61 cases.

In 25 (40.98 per cent) of the 61 cases hyaline, fibrinoid thrombi are present in glomerular loops (figs. 9 and 50); at times the thrombus fills a larger blood vessel entering the glomerulus (figs. 51, 52 and 53). In most of these kidneys the thrombi are few in number and found only after prolonged search. In only 4 kidneys could they be described as frequent or numerous; in no case did they form a prominent lesion. In these 25 cases there were only 2 in which some proliferation of the cells of the glomerular tuft did not occur. In other words the fibrinoid thrombi occurred in 23 (92 per cent) of the 25 cases in the presence of a diffuse proliferative cellular glomerular lesion.

As a rule, there is no reaction about the thrombus. Sometimes polymorphonuclear leucocytes have infiltrated the glomerular tuft in which fibrin thrombi occur or are present in the tissues about an obstructed entering blood vessel (figs. 52 and 53). The endothelial cells in the vessel obstructed by the fibrin thrombus do not seem to have proliferated; sometimes they seem to have degenerated.

Earlier observers have considered the lesion just described as embolic in origin. Later some have thought them to be thrombotic, the material making them up having originated locally. My own study indicates that they are the result of a thrombotic process. In some sections one sees areas of degenerated cells without nuclear staining in the midst of well staining cells of a glomerulus that shows cell proliferation (fig. 4). At times within a glomerular capillary are seen large cells with large vacuolated nuclei (fig. 8). Such degenerations might easily form the nidus for fibrin deposition and the formation of a thrombus. It is possible that bacteria may have been the prime cause of the degeneration that has preceded the fibrin deposit; if this is true, possibly a good term for them is embolic-thrombotic. In some glomeruli fibrin deposits can be seen between degenerated endothelial or epithelial cells; these certainly are not of embolic origin. Many

years ago Dr. O'Hare and I (5) described in the rabbit glomerular lesions like these fibrinoid thrombi in cases of subacute bacterial endocarditis in an occasional kidney damaged by subcutaneous or intravenous injections of uranium nitrate; in these there could be no probability of emboli playing a part. It seems highly improbable that what is seen in the glomeruli is in any large measure a broken off portion of valve vegetation. On the whole thrombosis seems most likely the usual process that is going on.

The part played by streptococci in the mechanism of these various glomerular lesions has been discussed extensively. As a rule, bacteria have been demonstrated infrequently in the glomeruli of these patients.

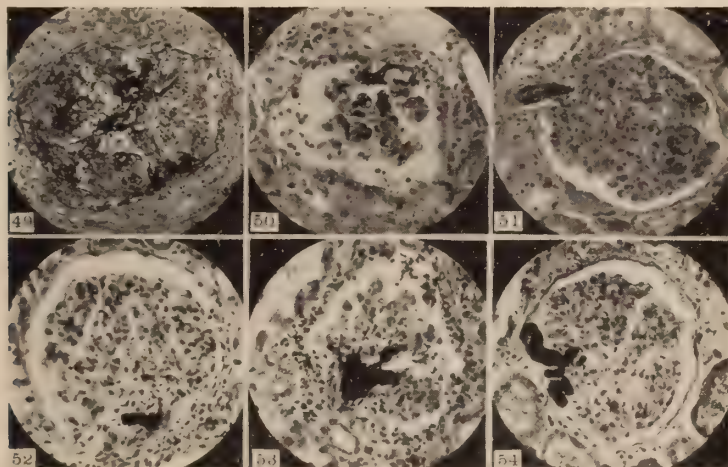


FIG. 49. Swollen, degenerated glomerulus infiltrated with leucocytes and fibrin and at one side generated epithelial crescent with fibrin and red blood cells; $\times 260$.

FIG. 50. Hyaline, fibrinoid thrombi in capillary loops; $\times 360$

FIG. 51. Hyaline, fibrinoid thrombus in afferent arteriole; $\times 360$

FIG. 52. Similar to Fig. 51; cells near thrombus degenerated and infiltrated with leucocytes; $\times 360$.

FIG. 53. Similar to Fig. 52; with more infiltrating leucocytes; $\times 360$

FIG. 54. Dense masses of cocci in blood vessels of glomerulus; latter in part degenerated, in part moderately cellular; $\times 360$.

I have seen them in sections from but 4 of the 61 cases (6.55 per cent) of this study. In these the cocci made up great masses of bacteria filling quite large glomerular capillaries (fig. 54) but causing no reaction in the capillary wall and surrounding cells. It looks as if shortly before or after death cocci for some reason had multiplied very rapidly to form great colonies of bacteria. It is fair to state, however, that the kidney tissues from my cases have not been stained by special methods to demonstrate bacteria, and so small groups of cocci easily may have been overlooked.

All of the focal lesions herein described varied much in frequency from kidney to kidney; usually fairly frequent, only rarely did they dominate the histological picture. In these kidneys tubular epithelium generally

showed granular degeneration of cytoplasm with pyknosis or disappearance of some nuclei. In the tubules granular debris and casts were frequent. Often tubules were filled with blood derived from lesions in the connected glomerulus. When glomeruli have been injured to the point of loss of function, the connected tubule shows an atrophy of its epithelium.

In the clinical study of this group of patients with fatal subacute streptococcus viridans endocarditis and post-mortem study of the kidneys the urine, with the exception of that from 11 patients (18.03 per cent), showed abnormalities. This would be expected, since all of these patients suffered from an infectious disease in which for many days fever, often of quite high degree, existed during a part of the twenty-four hour period, and at autopsy they showed lesions in the kidneys; actually it is surprising that any of the patients had excreted urine that was normal. The renal lesions, as already described, were of two types, 1) diffuse or general and 2) focal. The diffuse or general lesions were, besides the proliferative glomerular lesions and the thickening of the capillary basement membrane, in the nature of degeneration of different degrees in the tubular epithelium such as are found in febrile diseases. The focal lesions were "embolic-thrombotic" lesions in the glomeruli, atrophic and degenerative changes in the epithelium of tubules arising from seriously damaged glomeruli, hemorrhage into glomerular spaces and tubules and infarcts. For these individual lesions no pathognomonic urinary patterns were encountered that would permit a definite intra-vitam diagnosis of the type or types of pathological lesion to be found on post-mortem study beyond the presence at times of many red cells in the urine making it probable that the kidneys contained proliferative, cellular, diffuse glomerular lesions and some type of focal glomerular lesion, often along with other of the renal lesions already described.

Albuminuria, in amount ranging from the more frequent slightest possible trace or slight trace to the occasional large amount, was observed in all but 13 of the 61 patients, i.e., 78.69 per cent had albuminuria; 21.31 per cent were without it. This would be expected as albuminuria in slight amount usually is associated with prolonged fever of almost any cause and in larger amount usually accompanies lesions of the glomeruli.

Cylindruria, on the other hand, was not a prominent feature. A few hyaline or granular casts, as a rule, were found, but in none of the patients were casts very varied in kind or numerous in number. In contrast blood cells were seen in the urine sediment in three-fourths of the patients, and in nearly half of these the sediment was described as showing numerous red blood corpuscles or as loaded with them. The larger number of red cells, as a rule, appear for a short time and then decrease or disappear or are present only for a short time before death. If daily examinations of the urine of these patients had been made, it is probable that more would have shown periods of microscopic hematuria. Some of the patients were

in the hospital only for short periods of time, and these had few examinations of the urine. In many of the kidneys, which during life had excreted on occasions urine containing many red cells, infarcts, glomerular thrombi and proliferative glomerular lesions were found. Of these infarction and glomerular "thrombi" probably were least important in causing the escape of red blood cells, since in the urine of half of the patients with renal infarcts no red blood cells or only a rare one were seen, and this was true also of two-thirds of those with glomerular thrombi. Furthermore, infarcts were present in all of the patients whose urine was normal, and fibrinoid glomerular thrombi in four of the eleven that had normal urine. Thus the excretion at times of a urine containing numerous to very large numbers of red blood cells suggests the presence of a diffuse or focal proliferative cellular glomerular lesion rather than the presence of infarction or fibrinoid glomerular thrombi.

Seventeen (26.88 per cent) of the 61 patients showed decreased renal function as indicated by decreased phenolsulphonaphthalein excretion or by elevated blood urea nitrogen. In only 7 of these was the change from normal great enough for possible symptoms of uremia; no one of these patients, however, became definitely uremic before death.

SUMMARY

The kidneys from 61 patients dying from subacute streptococcus viridans endocarditis showed 1) slight swelling and edema, practically in all, 2) focal hemorrhages, causing the "flea-bitten" kidney in 13.11 per cent and 3) areas of infarction in 91.8 per cent. Microscopic study shows a diffusely distributed, proliferative, cellular, glomerular lesion, analogous to the lesion in acute intracapillary proliferative glomerulonephritis in 80.32 per cent of the cases and diffusely distributed, hyaline thickening of the walls of the glomerular capillaries in 16.39 per cent; the latter was the only lesion in 4 of the 10 kidneys, so that 85.24 per cent of the cases showed a glomerular lesion diffuse in distribution. Five types of focal glomerular lesions were seen; 1) proliferation of the capsular epithelium, so-called epithelial crescents, in 36.06 per cent of the kidneys; 2) focal fibrous lesions, chiefly projecting into the capsular space of the glomerulus from the capsule, sometimes situated within the glomerular tuft, in 26.23 per cent of the kidneys; 3) complete disorganization of glomeruli, an occasional lesion; 4) hyaline fibrinoid thrombi in glomerular vessels in 40.98 per cent of the kidneys, and 5) masses of bacteria in glomerular capillaries in 4 cases (6.55 per cent). All of these focal lesions were present in varying frequency in sections from different kidneys; only very rarely did they dominate the histological picture. They occurred only very rarely in glomeruli without other lesions.

Albuminuria was present in 78.69 per cent of the patients. Cylindruria was not prominent, a few hyaline and granular casts being the rule. A

considerable microscopic hematuria was found in 75 per cent of the patients, usually intermittently for short periods of time or shortly before death. The excretion at times of a urine containing in the sediment numerous to very large numbers of blood cells suggests the presence of a diffuse or focal, proliferative, glomerular lesion rather than the presence of infarction or fibrinoid glomerular thrombi. Decreased renal function as indicated by decreased excretion of phenolsulphonephthalein or by elevated blood urea nitrogen was observed in one-fourth of the patients, but in none of them did this result in symptoms of uremia.

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AGENESIS OF THE CEREBELLUM (VERIFIED BY OPERATION)

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All of the hitherto reported cases of agenesis of the cerebellum are based on post mortem material. As such there is a completeness and a certain finality in the description of the gross and the microscopic studies. Some few of the authors have been able to give the clinical history so that a grasp of conditions as they existed in life may be obtained.

As Baker and Graves (1) point out, complete agenesis is extremely rare. The maldevelopment varies from absence of the entire cerebellum to a partial defect of one hemisphere. The authors also note that a distinction between atrophy and agenesis must be made. They give a brief review of the cases reported up to 1931. More recently Rubinstein and Freeman (2) in reporting the life history and the post mortem gross and microscopic studies, discussed the question of compensation for the cerebellar deficiencies.

The chief interest in the case to be described is that a maldevelopment was suspected prior to the air studies, that these confirmed the suspicion. Moreover, signs of increasing intracranial pressure made operation imperative, and the condition of agenesis was verified by the operation.

CASE REPORT

History (Adm. 450969). In January 1940 a thirteen year old boy was admitted to the Neurological Service because of headaches of ten weeks' duration. He was the fourth child delivered normally after sixteen hours of labor. His development was slow, he did not walk until the age of nineteen months and did not speak more than a few words until he was over four years old. His school work was such as to keep him in an ungraded class. However, he managed to get along very well with other children. He suffered headaches, which necessitated hospitalization; these were infrequent at the onset but later were a daily occurrence; they would usually come on late in the day and last for several hours. Associated with the headaches was the subjective feeling of falling, always toward the left. On one occasion there was diplopia and once vomiting. For the entire period of ten weeks he complained of constant fatigue and showed little inclination to play.

Examination. The boy was shy and obviously subnormal mentally, though he cooperated fully in the examination. This showed his speech to be monotonous and infantile. His head had a peculiar elongated shape. A tympanitic note was obtained throughout on percussing the head. Both pupils were dilated, the right more than the left, but they both reacted to light and in accommodation. There was a left external rectus weakness. Both fundi showed papilledema of one diopter, with dilated retinal veins. There appeared to be a slight left central facial weakness. The gag reflex was depressed. Alternating and skilled acts were poorly carried out

especially with the left hand. Some observers thought that the left arm and leg were weaker than the right. The deep reflexes were depressed in the upper extremities and hyperactive in the lower extremities. No Babinski sign or other abnormal reflexes were found.

Laboratory Data. The cerebrospinal fluid pressure measured 330 mm. water with an Ayala index of 5.7. The cells, total protein and serology showed no deviation from the normal. X-ray studies of the skull revealed a large skull with some separation of the fronto-parietal sutures.

Operation. On January 16, 1940 Dr. Sidney Gross carried out ventriculography through bilateral occipital burr holes. The dura appeared tougher than normal and when it was incised a thin membrane presented itself beneath it. When this was opened, clear fluid escaped in large amounts. At first a bilateral subdural hydroma was suspected, but no underlying brain tissue could be seen. No air was injected, but sufficient air replaced the escaping fluid to provide satisfactory x-ray studies. These showed in the antero-posterior views tremendously dilated lateral ventricles; in the lateral view these appeared to be crowded forward and upward by a cavity containing air (fig. 1). This latter occupied the posterior fossa and the posterior portion of the middle fossa. In the vertex down position (fig. 2) the third ventricle was visualized, and extending from it could be seen the iter, the caudal end of which opened into the air filled cavity in the posterior fossa. Air was seen in the spinal canal to the second cervical vertebra.

Postoperative Course. The immediate postoperative reaction was very stormy. The boy was drowsy and vomited frequently. Lumbar punctures yielded xanthochromic cerebrospinal fluid. For several days he improved, but then he began to have bouts of agonizing headaches at which times there would be pronounced bulging at the site of the burr holes. Temporary relief was afforded by the evacuation of fluid through these openings. These bouts appeared at more frequent intervals and the papilledema advanced so that operation for the relief of pressure became imperative.

Operation. From the clinical picture, an exploration of the posterior fossa seemed indicated. But it was known that the fluid had been obtained from the burr holes made over the normal site of the occipital lobes. Moreover, this area seemed continuous with, or part of, the air-filled cavity in the posterior fossa, and the tentorium appeared to be situated abnormally high. Therefore, on February 6, 1940, under local anesthesia, an occipital flap was made (fig. 3). As events transpired the exposure was adequate, though a trifle cramped. The quadrilateral bone flap was turned outward and the dura opened in a similar fashion. The thin membrane noted at the previous procedure was encountered beneath the dura and loosely attached to it. When the thin membrane was opened and a huge amount of cerebrospinal fluid removed, a similar membrane was seen which extended from the first membrane at right angles in the midline and divided the upper part of the cavity into two chambers.

The outer attachment of the tentorium was well above the upper limit of the bone flap. This fixed the attachment about half way between the normal positions of the coronal and lambdoid sutures. The dividing membrane was torn through converting the two cavities into one. In tracing the rest of the membrane it was found to line the entire inner surface of the dura of the posterior fossa and to extend down into the spinal canal, then it turned upward, forming thus a closed pocket below. As it came up it spread out over the brain stem and the cranial nerves. It was intimately attached to the medulla and thinned out or disappeared over the pons. It was very vascular, but so thin that the brain structures could be seen through it. There was thus seen the open fourth ventricle and the pons. At the upper end of the latter, was

a nipple-like opening from which escaped cerebrospinal fluid. This was believed to be the lower end of the iter, as noted in the ventriculogram.

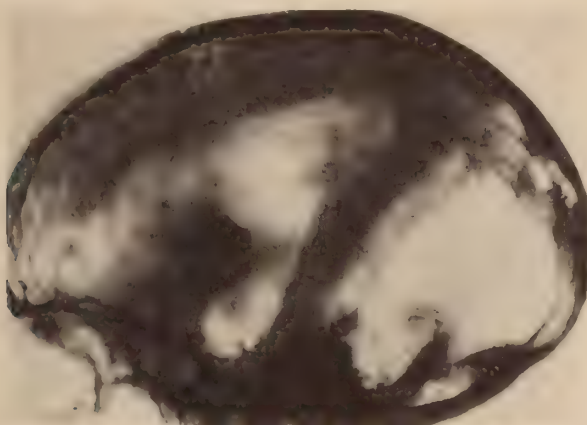


FIG. 1. Dilated lateral ventricles and air-filled cavity in posterior fossa.

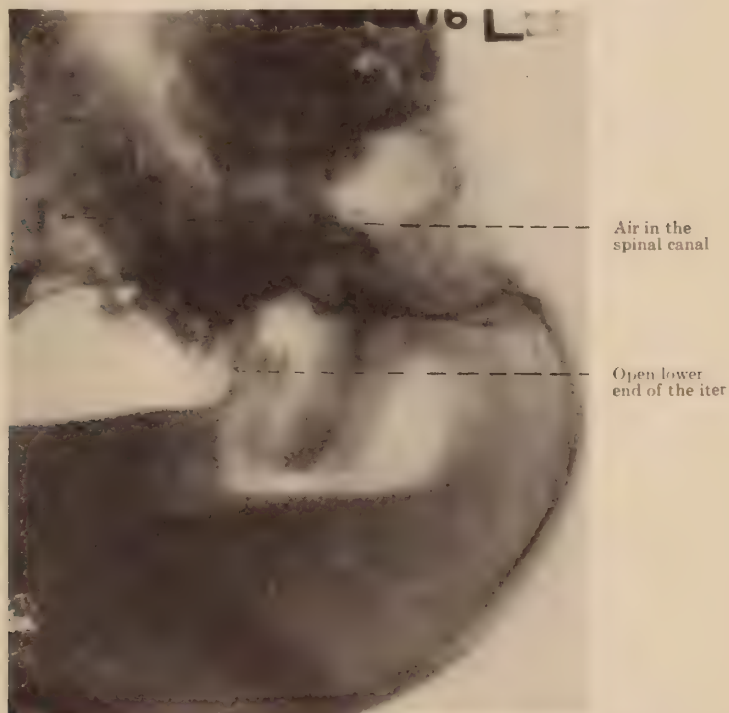


FIG. 2. Vertex down position showing iter communicating with air-filled cavity in posterior fossa

On either side of the brain stem was a small nubbin of brain tissue less than two centimeters in diameter which was taken to be the rudimentary cerebellar lobes. These resembled somewhat the flocculus and were the only structures seen that could in any way be considered cerebellum (fig. 4).

Between clips the membrane was excised except where it was adherent to brain tissue. It was torn through in the region of the eighth nerve on the left and was also

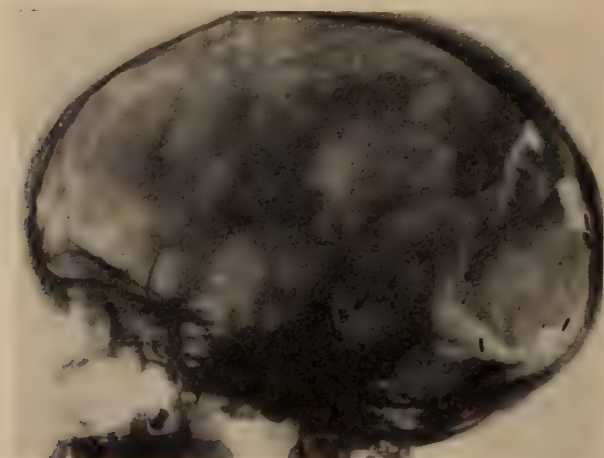


FIG. 3. Postoperative skull plate to show position of flap

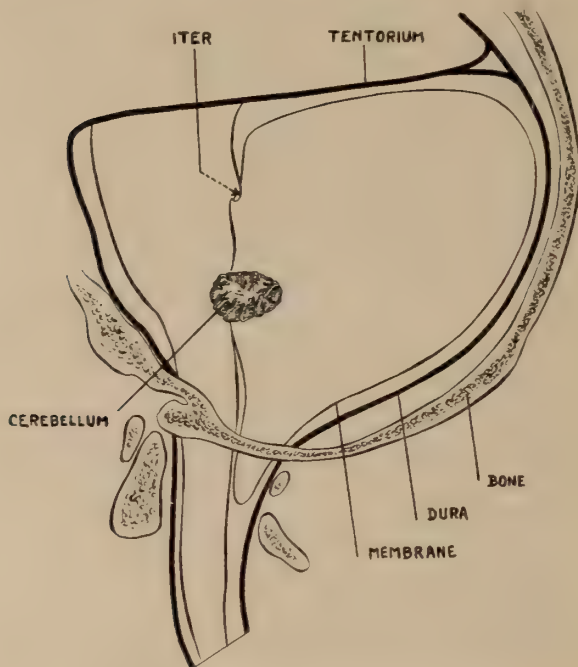


FIG. 4. Diagram of operative findings

torn through into the spinal canal. The dura was tightly sutured, the flap wired in place and the scalp closed. The excised membrane was studied by Dr. J. H. Globus who reported as follows: "Sections of the 'cyst wall', stained by the various histo-

logical methods, show a layer of vascular connective tissue in close approximation to brain tissue. The first layer resembles undifferentiated leptomeninges and is densely cellular. The second layer contains both neuronal and glial elements with remnants of an ependymal zone along its free border. The neuronal elements at times show lamellar arrangement with long processes directed toward the meningeal surface. In some sections there are small collections of myelinated fibers arranged parallel with and near the ependymal surface. At times the ependymal cells occur clumped. In both brain and meningeal layers there are occasional blood vessels surrounded by aggregates of small cells, an arrangement resembling that seen in the foetal brain. Where the two layers join there is a wavy outline interrupted by interdigitations of connective tissue which penetrate the brain tissue for varying distances, occasionally accompanying small blood vessels. At times connective tissue fibrils appear to penetrate deep into the brain tissue; then again, processes from the glial elements are lost among the fibrils in the connective tissue layer. There are a few bipolar cells which send one process to the meningeal surface and another to the ependymal surface. In some sections the nervous layer gives place to the fusion of the ependymal and meningeal layers to form a choroid plexus-like structure. Diagnosis: Blastomatous malformation with retention of primitive neuromeningeal organization resulting in the formation of an encephalomeningocele."

Postoperative Course. The immediate postoperative course was very unsatisfactory. In addition to fever, which for the most part ranged between 101°F. and 103°F. (on a few occasions higher), the boy vomited frequently. He had to be fed by tube. He found the greatest comfort in lying face down. There was considerable bulging at the site of the original burr hole exploration. Lumbar punctures controlled this. This procedure, or aspiration of fluid through these holes, relieved the headache which was a rather constant complaint. It was not until a month after the operation that the boy was really comfortable and could be allowed out of bed. At this time the fundi were much improved, he had no ataxia in the upper extremities, but his gait was very unsteady. Fifteen months after discharge, he is symptom-free and practically without abnormal signs.

COMMENT

The operative findings demonstrated that the tentorium was displaced upward so that it must have reduced the space of the middle fossa, that, except for a small nubbin of tissue, the cerebellum was completely absent, that the lower end of the iter opened into a large cavity and that the fourth ventricle had no roof as this structure is understood. In spite of these defects the patient, both prior to the acute episode and in the months following the operation, has been able to compensate very well. He is not normal in mental development, but he is able to engage in many of the activities of a boy of his age. In this respect he resembles some of the cases reported, as for example that of Rubinstein and Freeman (2). The symptoms manifest in the acute episode were those commonly seen in tumors of the posterior fossa. In fact, the mechanism to all intents and purposes was the same. The thin vascular membrane which was found lying just within the dura formed a sac, into which the cerebrospinal fluid entered through the patent iter, and from which there was no apparent free exit. The microscopic study of this membrane suggested that it represented the structures of the roof of the fourth ventricle as they existed

at an early stage of the development of the cerebellar plate. For in it were present in zones, ependymal cells, choroid plexus formation, glial and neuronal elements and leptomeninges. In other words, the cavity represented the interior of the fourth ventricle. A similar picture is graphically described by Bucy (3) in dealing with hydrocephalus due to occlusions of the foramina of Magendie and Luschka. He points out the elevation of the tentorium and the reduction in size of the cerebellar lobes. Dandy (4), writing on the same subject, states the cerebellar lobes may be represented by small "nubbins".

The occurrence of multiple congenital defects in the same individual has been noted many times. Agenesis of the cerebellum and absence of the foramina of Magendie and Luschka may be part of one and the same aplastic process, but not necessarily so. Not every agenesis of the cerebellum is associated with hydrocephalus, and the majority of cases of hydrocephalus involving the fourth ventricle have recognizable cerebellar lobes. Salter (5) reported one instance of unilateral absence of a cerebellar lobe with extreme hydrocephalus in which the obstruction lay cephalad to the fourth ventricle.

The degree of hydrocephalus in our patient points to a long-standing obstruction which, however, was probably not complete. Neither the size nor the shape of the boy's head was that of a congenital hydrocephalus. The acute episode marked the failure of compensation of circulation of the cerebrospinal fluid, possibly the complete occlusion of an existing communication of the fourth ventricle with the subarachnoid space. This, in turn, provided the indication for operative intervention.

SUMMARY

A case is herein reported of a thirteen year old boy who presented the clinical picture of increasing intracranial pressure. At operation he was found to have an agenesis of the cerebellum with complete absence of the normal roof of the fourth ventricle. The latter was probably represented by a thin vascular membrane in close contact with the dura, and forming a sac filled with cerebrospinal fluid. Operative procedures providing for the escape of this fluid brought about an amelioration of the symptoms.

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SURGICAL PROBLEMS IN THE TREATMENT OF GASTRIC ULCER

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Even with the best available diagnostic facilities, the differentiation between benign and malignant lesions of the stomach may present difficulties. Diagnostic errors are not infrequent. In 1936 Klingenstein (3) collected 165 cases of chronic gastric ulcer which were operated upon at The Mount Sinai Hospital, New York, from 1925 to 1935, and in 20 per cent of these a diagnosis of carcinoma of the stomach was made by the roentgenologist. Twelve per cent, in which a benign ulcer was diagnosed, were proven to be malignant subsequently. In the past three and a half years, during which 28 consecutive ward cases of gastric ulcer were resected, there were 6 additional cases in which a benign ulcer was suspected but in which a carcinoma was present at the time of exploration.

CASE REPORTS

Case 1 is rather typical of this group. The patient, a comparatively young man, was under observation and treatment for an ulcer of the stomach for over one and a half years. Operation unfortunately disclosed a well advanced carcinoma with lymph node metastases.

Case 1. History (Adm. 475800). This was the first admission of a 45 year old Polish male chemist who one and a half years before entry began to have acid eructations, retrosternal and epigastric burning pain about two hours after eating. X-ray examination of the stomach revealed an ulcer which was thought to be benign. This responded to a prescribed medical regime. Three months prior to admission his symptoms recurred and he again responded to medical treatment. Later he was referred to the hospital from the Out-Patient Department for a recurrence of his symptoms, absence of free hydrochloric acid in the test meals, and x-ray evidence of a 4 cm. ulcer crater with an irregular base along the lesser curvature of the stomach.

Laboratory data. Hemoglobin 94 per cent; red blood count, 4,700,000; white blood count, 7,900 with a normal differential. The urine was negative. The blood Wassermann reaction was negative. Gastric analysis showed normal free and combined acidity. Gastroscopy revealed the proximal edge of an ulcerated mass on the lesser curvature and posterior wall at the angularis. The base of the ulcer, antrum and pylorus could not be seen. The stool was negative for guaiac.

Operation. Exploration was performed under spinal anesthesia through a median epigastric incision. It revealed a deeply ulcerated, infiltrating colloid carcinoma of the stomach with extension into the mesentery and involvement of the glands in the region of the re-entrant angle along the lesser curvature. A typical retrograde subtotal gastrectomy was performed, and ante-colic Hofmeister termino-lateral gastro-jejunostomy completed the procedure.

The pathologic report revealed a colloid carcinoma with extension into mesentery, and early involvement of lymph nodes.

Course. The postoperative course was entirely uneventful, and patient was discharged seventeen days after operation.

Case 2 is of interest because in the absence of free hydrochloric acid in the aspirated gastric contents, and positive x-ray findings, a carcinoma was suspected. Even at the time of operation the diagnosis of malignancy was made by the surgeon. However, the pathologic examination disclosed a benign lesion.

Case 2. History (Adm. 476464). This was the first admission of a 45 year old man who was apparently well until twenty months prior to entry when he noted the development of epigastric distress, before and after meals, relieved by food and soda. This became worse but was not associated with vomiting. Seven months previously he was hospitalized at another institution in which, on conservative treatment including milk drip and amphojel, marked improvement was soon noted, with a decrease in the size of the ulcer on x-ray examination. However, since that time his diet had been irregular and the pain had become recurrent. Several days before admission there was a hematemesis of several ounces for the first time. The patient had lost twenty pounds in weight during a period of three months. At the age of 20 he contracted syphilis and was treated for two years.

Examination. The patient was an emaciated man. The pupils were irregular and unequal and did not react to light or in accommodation. The lungs were clear. The heart was normal. The blood pressure was 110 systolic and 64 diastolic. There was slight tenderness in the epigastrium. There was a small supraumbilical hernia. Neurological examination revealed diminished deep reflexes in the legs, positive Babinski and confirmatory on the right.

Laboratory data. Hemoglobin 80 per cent. White blood count 8,000 with normal differential. Blood Wassermann reaction, 2 plus. Cerebrospinal fluid Wassermann reaction, negative; colloidal gold, negative; globulin, negative. Blood urea nitrogen, 12 mg. per cent; blood sugar, 60 mg. per cent; chloride, 620 mg. per cent; total protein 4.5 grams per cent. Carbon dioxide combining power, 67.5 volumes per cent. Electrocardiogram showed no abnormal changes. Gastric analysis revealed a very small amount of acid. A gastrointestinal series showed a smooth projection on the lesser curvature of the stomach just at the re-entrant angle. The appearance was suggestive of an ulcerating neoplasm.

Because of the lack of free acid in the Rehfuß test together with the x-ray findings, and the fact that gastroscopy showed an ulcerating lesion 8 cm. below the cardia, which was interpreted to be malignant, a tentative diagnosis of a carcinoma of the stomach was made.

Operation. Operation was performed under spinal anesthesia through a median epigastric incision. A firm, indurated lesion was found at the re-entrant angle along the lesser curvature of the stomach. A retrograde subtotal gastrectomy of the Billroth II type with an ante-colic, termino-lateral gastro-jejunostomy of the Hofmeister type was performed. The abdominal wound was closed in layers.

Pathologic report was chronic peptic ulcer of the stomach with no evidence of tumor.

Course. The postoperative course was entirely uneventful.

However, any gastric ulcer intrinsically possesses the possibility of undergoing carcinomatous transformation. In our experience this is rare, and

according to Klein (2) it occurred only twice in the careful pathologic study of 140 cases of chronic gastric ulcer.

Case 3. History (Adm. 457151). For fifteen years the patient had complained of periodic epigastric pain associated with a "choking feeling" two hours after meals, and relieved by food and alkali. Because of an exacerbation of pain in January and March, 1940, associated with anorexia and loss of ten pounds, he finally decided to determine the cause of these symptoms and was referred to the Consultation Service of The Mount Sinai Hospital in May, 1940.

A gastrointestinal series at that time revealed a large gastric ulcer on the posterior wall just above the re-entrant angle with a protruding pocket two inches in diameter on the lesser curvature. There was also a 30 per cent residue of barium at six hours. Because of its large size, a carcinoma was suspected, but an attempt at gastroscopy was unsuccessful because of a marked kyphoscoliosis.

The patient was advised to enter the hospital, where a therapeutic test was carried out, using the amphojel phosphate continuous intra-gastric drip during the day between meals, and throughout the night. The pain rapidly disappeared. The patient gained weight and there was a notable increase in appetite.

Three weeks after this therapy was begun a gastrointestinal series showed a marked decrease in the size of the ulcer from 2 inches in diameter to $\frac{5}{8}$ inches, and another series six weeks after the intra-gastric drip was started showed still further diminution with only a very shallow crater. There was no gastric retention. It is of interest that after the patient had been on this therapy for two weeks, discontinuance of the amphojel for 24 hours produced a sharp re-exacerbation of pain.

The patient was discharged after seven weeks, in July, 1940, having gained seven pounds and being much improved. The only other significant findings were a free acid of 40 and total acid of 60. The stools were negative for guaiac. The hemoglobin was 89 per cent. A diagnosis of essential hypertension was made, because of the presence of a soft, systolic apical murmur. The blood pressure was 160 systolic and 94 diastolic, and liver was enlarged to two fingers below the right costal margin.

The patient continued to do well at home for several months until October, when the symptoms recurred following an upper respiratory infection. The pains were worse than they had ever been, being described as "terrific" and were rather severe at night. However, he did not consult a physician until January 10, 1941, when he also complained of belching after meals and a fear of eating because of the pain. Except for a blood pressure of 148 systolic and 98 diastolic and lower substernal tenderness, there were no other significant findings on physical examination. His weight had been maintained.

Despite a strict dietary regime and medication, the pain continued and started to radiate through to the back. A gastrointestinal series on January 21, 1941 showed a stomach with a large layer of hypersecretion and an ulcer at the previous site, $1\frac{1}{2}$ inches in diameter, with a marked incisura opposite the ulcer. There were no other findings, and gastric mobility was normal.

In view of the persistent symptoms, lately radiating to the back, the failure of permanent response to the strictest type of in-bed medical therapy, and the age of the patient, he was referred to surgery with a diagnosis of gastric ulcer penetrating into the pancreas, with possible malignant change.

Operation. A subtotal gastric resection with Hofmeister ante-colic termino-lateral gastro-jejunostomy was performed under ethylene and avertin anesthesia. The pathologic report was as follows: "At the mid-portion of the lesser curvature was a circular lesion 3 cm. in diameter and about .6 cm. in depth with a necrotic ulcerated center. The edges were indurated and elevated above the general level of the mu-

cosa. The mucosa at the periphery of this lesion was granular in nature and somewhat indurated. At the base of the lesion on the serosal surface there was scar tissue marking the site at which penetration onto the capsule of the pancreas had occurred. The lesion microscopically revealed an adenocarcinoma with a chronic peptic ulcer. The lymph nodes were not involved."

Course. Despite the presence of a severe kyphoscoliosis in an individual with arteriosclerosis with hypertension, and except for a postoperative pneumonia promptly controlled by sulfapyridine, he made an uneventful recovery.

The frequency of carcinomatous ulcers of the stomach may be gauged by the fact that during the past three and a half years, 126 of these cases were explored. Unfortunately, only 45 per cent were found to be operable, and in this group the lymph nodes were involved in 50 per cent. It is a sad commentary on medical practice that 17 per cent of these patients had previously been treated for dyspepsia for varying periods of time, and not a few had received a course of medical treatment for a so-called "gastric ulcer".

These percentages are of more than academic interest. They call attention to the fact that no patient should be diagnosed empirically as dyspepsia and dismissed without the benefit of a thorough investigation. These figures emphasize quite definitely that a diagnosis of gastric ulcer should not be made until certain well established criteria have been fully satisfied clinically, gastroscopically, roentgenologically and therapeutically, i.e., a recession or disappearance of the ulcer pocket after a three week period of medical treatment. However, it must not be forgotten that some malignant ulcers too grow smaller under appropriate diet, with a temporary disappearance of all symptoms. Therefore, it is of paramount importance that a frequent and careful checkup be made in patients with a gastric ulcer. It is only in this way that an early carcinoma may be recognized.

It is universally agreed that the treatment of gastric ulcer is primarily medical, and that the majority of cases respond readily to dietetic measures. But all cases are not medical problems and there are indications for surgery in addition to the suspicion of malignancy. Operation may be urgently necessary in those patients presenting the acute symptoms of a sudden perforation. A simple closure of the ruptured ulcer is all that is usually done at this time. We do not advocate a gastroenterostomy or a gastric resection at this stage. However, we feel quite strongly that patients suffering from an acute, severe hemorrhage do not present an urgent surgical problem. We are not in accord with the dictum that patients over forty-five suffering from a massive hemorrhage should be operated upon within the first twenty-four hours. These cases are treated conservatively by the Muelengracht regime, delaying surgery until the acute episode has completely subsided and the physical condition of the patient has materially improved. Occasionally a patient will die from acute hemorrhage, but surgery in this type of case might also prove to be as disastrous.

Fortunately, in our present series we were not forced to operate upon any case with hemorrhage during the acute stage.

The chronic refractory cases may be ascribed to those penetrating, callous ulcers which occupy the pyloric and prepyloric region resulting often in an organic stenosis; to perforating lesions situated in the antrum, in the lesser curvature, near the re-entrant angle, and in the cardia. All these cases which have not responded to medical treatment require a careful preoperative preparation with adequate fluids, a liberal high protein diet with vitamins, and if anemia is present, repeated blood transfusions. While all prepyloric and pyloric ulcers are routinely explored, because clinically it is extremely difficult to differentiate between a benign and a malignant ulcer in this region, cases with pyloric stenosis require special preoperative preparation. Stomach lavages are given until the gastric dilatation with its retention has been materially diminished, and parenteral fluids of saline are administered until the fluid balance is maintained and the alkalosis which may have been present has been definitely corrected.

It is those cases which are complicated by repeated hemorrhage, by long standing pyloric stenosis, by high lying penetrating cardiac ulcers, and by previous gastric surgery which contribute to a high surgical mortality. If the surgical mortality is to be kept within reasonable limits there must be closer cooperation between internists, gastroenterologists, and surgeons. Cases which do not respond adequately to treatment should be referred for operation before more serious complications have developed, complications which may turn the odds against the benefits of surgery.

Gastric operations are best performed under spinal anesthesia supplemented by intravenous pentathal if necessary. However, regardless of the anesthetic employed, the incidence of postoperative pulmonary complications is extremely high. These contribute undoubtedly to the postoperative mortality and morbidity.

Many operations have been advocated in the treatment of gastric ulcer. Gastroenterostomy as a definitive procedure for ulcer, especially the cardiac variety, has not been a satisfactory procedure in our hands. While it is true that the gastric acidity is diminished due to the neutralizing effects of duodenal regurgitation, the symptoms are not relieved permanently. Local excision of a high lying chronic calloused ulcer, supplemented by gastroenterostomy, is technically difficult, and often extremely dangerous. Dissection in this chronically inflamed tissue, and the insecurity of the suture line obtained under these conditions often leads to a fatal peritonitis. A partial gastrectomy of the "sleeve" type has been abandoned because it interfered too often with the normal functions of the stomach.

The procedure of choice in this clinic is a subtotal gastrectomy of the Bilroth II type with restoration of intestinal continuity by a Hofmeister termino-lateral gastro-jejunostomy. The anastomosis may be made either

anterior or posterior to the colon. This operation which removes the pylorus and antrum has certain advantages. It removes the ulcer radically, and if the resected specimen should prove to be malignant the chances of cure are materially enhanced. It produces an anacidity in most cases, which apparently is instrumental in safeguarding patients against future gastric and gastro-jejunal ulceration. But subtotal gastrectomy with removal of the ulcer is not practical in all cases. Chronic ulcers situated along the lesser curvature near the esophagus, or located high in the posterior wall of the stomach penetrating into the pancreas cannot be resected without a prohibitive mortality. In order to extirpate these, a complete gastrectomy would be necessary. For this type of lesion Madlener (4) in 1923 suggested a simple pylorectomy leaving the ulcer *in situ*. Flörcken (1) subsequently advised the removal of the pylorus and antrum distal to the ulcer and called the procedure a "palliative gastric resection". This operation which is simple and effective, is justified both experimentally and clinically. A subtotal gastrectomy, especially in cases of gastric ulcer, produces a permanent anacidity. In its presence any ulceration in the remaining gastric segment apparently heals spontaneously.

Case 4 is typical of a group of cases in which a palliative gastric resection was performed.

Case 4. History (Adm. 416481). This patient's history dated back one year, at which time he developed the characteristic symptoms of a gastric ulcer. Inasmuch as ambulatory medical treatment failed to relieve his pain, he was admitted to the hospital and placed upon a Sippy diet and a milk drip. His symptoms were temporarily relieved for about three weeks and he was discharged. However, he soon returned because of a recrudescence of his symptoms and he was re-admitted.

Examination. The patient was an emaciated, middle aged man. The right eye had been enucleated. There were findings of a chronic bronchitis and emphysema. There was a systolic murmur at the cardiac apex, and the heart was slightly enlarged. The blood pressure was 160 systolic and 90 diastolic. There was obvious sclerosis and tortuosity of the peripheral vessels. There was moderate tenderness in the epigastrium. The liver was palpable 2 cm. below the costal margin. The hemoglobin was 98 per cent. A preoperative Rehfuess test meal revealed 62 per cent free acidity and 74 per cent total acidity after administration of $\frac{1}{2}$ cc. histamine. X-ray examination revealed a penetrating ulcer of the lesser curvature of the stomach quite proximal to the re-entrant angle.

Operation. Operation was performed on November 13, 1937, under avertin and ethylene anesthesia. The stomach was normal in size, but in the cardiac area, in the region of the lesser curvature extending posteriorly, there was a hard indurated mass which invaded and seemed attached to the tail of the pancreas. A palliative subtotal gastrectomy of the Hofmeister type with a posterior retro-colic gastro-enterostomy was performed. The pathologist reported that 14 cm. of the lesser curvature and 16 cm. of the greater curvature had been removed, and that a chronic gastritis was present.

Course. The postoperative course was complicated by a bilateral basal bronchopneumonia.

Patient has been seen repeatedly, the last time being September 24, 1941. He has gained 30 pounds in weight and has had no gastric complaints. X-ray and gastro-

scopic examination failed to reveal the presence of the ulcer. A test meal showed an anacidity.

These patients have lost their symptoms, and have gained weight. The gastric analyses have failed to reveal any free acid. X-ray and gastroscopic examinations have not demonstrated the presence of an ulcer. This operation may be condemned by some because it is futile if the ulcer which has been left *in situ* should prove to be malignant. This is essentially true, but when an ulcer of this type reaches the stage of penetration and infiltration into adjacent tissues, it is radically inoperable if it is malignant.

SUMMARY

In this series of 28 consecutive ward cases of gastric ulcer, a subtotal gastrectomy was performed in 23, a palliative gastric resection in 5. There were 2 deaths, 1 on the second day, presumably due to a fulminating pneumonia, and 1 on the fourth day, in which an autopsy disclosed an extensive pneumonitis.

The follow-up results in all cases have been excellent.

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THE HEART IN FAT EMBOLISM

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We have come to realize of late that attacks of coronary occlusion with myocardial infarction are not so very rare in surgical wards as a post-operative complication (1, 2), and it has been rather taken for granted that such attacks represent instances of coronary thrombosis. In most cases that assumption is doubtless fully justified.

The occasional occurrence, however, of one or more attacks suggesting acute coronary closure, in patients who have had an operation or an injury that might well have given rise to fat embolism, has raised in my mind the question as to whether such fat embolism ever produces symptoms which can be recognized as due to coronary embolism. This question is not one merely of academic interest; it might conceivably have some bearing on the subject of prognosis. Accordingly it has seemed worth while to review the literature of fat embolism in the hope of finding an answer to that question.

Beneke (3) states that embolism resulting from the displacement of particles or fragments of fat from injured fatty tissue is probably the most frequent of all the forms of embolism. Such emboli represent, moreover, almost the only type, aside from tissue cells, that is known to pass readily through the pulmonary capillaries and to find lodgement in the smaller branches of the general arterial system.

First recognized in man by Zenker (4), the condition gained greatly in importance and interest by the recognition soon afterward, by von Recklinghausen and his pupil Busch (5), of the important relation of such emboli to bone injuries. Since that time a surprisingly large literature has arisen, covering the pathological, the clinical and the experimental aspects of the subject.

While injuries to bone—fractures, crushing, orthopedic operations—and the dislodgement of fat from the bone marrow are much the most frequent and important source of such emboli, they have often been found in various other conditions in which there has been injury to or infection of fatty tissue. Thus, fat emboli have been found after severe contusions with injury to the subcutaneous fat, after eclamptic and other convulsive seizures, with inflammation of fatty tissue, in acute osteomyelitis, after extensive burns and after violent concussion even when no fracture has occurred.

The transfer of such fat particles occurs chiefly through the venous

circulation, but fat is mobilized also, though much more slowly, by way of the lymphatics and the thoracic duct. While the lungs bear the brunt of the embolic attack, a certain amount of the circulating fat seems always to pass through the pulmonary capillaries and to find its way into the general circulation. In many instances this amount is too small to produce recognizable symptoms; but not infrequently the clinical picture is determined rather by the arterial emboli than by those in the lungs. The amount of fat passing through the lung capillaries varies greatly and is determined by a number of factors, such as the amount of fat mobilized, the fluidity of the fat, the width of the lung capillaries, the driving force of the right ventricle, etc. Fat which passes through the pulmonary capillaries is distributed widely through the arterial system, but has been found most frequently and most abundantly in the arterioles and capillaries of the brain and the meninges and in those of the heart, the kidneys and the spleen.

Clinical features. It is customary to divide cases of fat embolism into two main types, the pulmonary and cerebral. Of these the latter is the more interesting and presents the more striking and characteristic symptoms. Cases of the pulmonary type usually manifest their symptoms very early (often within a few hours), are generally of short duration and frequently cannot be diagnosed during life. They have been subdivided into an "apoplectiform" type—fulminating cases with cyanosis, dyspnea, and circulatory collapse—and more slowly developing cases, with symptoms suggesting a diffuse pneumonia or with pulmonary edema, bloody sputum and heart weakness as the prominent symptoms.

Cases of the cerebral type present three more or less distinct stages; 1) an interval, from a few hours to a day, following the fracture or bone injury, free from cerebral symptoms, during which there may or may not be pulmonary or cardiac symptoms; 2) a stage of somnolence or apathy, and 3) a comatose stage, in which in addition to stupor or coma there may be delirium, rigidity, convulsions, clonic movements, Cheyne-Stokes breathing, changes in the reflexes, and rarely, paralyses. Signs of increased intracranial pressure such as slow pulse, choked discs, etc. are lacking.

Such cerebral cases may, of course, be associated with pronounced pulmonary symptoms, but often these latter are so slight that the clinical picture is dominated by the symptoms referable to the central nervous system.

Not all such cerebral cases progress to a fatal issue even when the symptoms are very severe. The literature contains a good many instances of recovery in cases in which the cerebral disturbances have been profound.

The behavior of the temperature has been the subject of discussion and disagreement. Scriba (6) believed that a subnormal temperature was characteristic of fat embolism. On the other hand, a number of observers

have found that a good many of the cases are accompanied by high fever. Rückart (7), the last to study this aspect of the subject, harmonizes these divergent views by pointing out that in the cerebral cases high fever is the usual finding, whereas in the pulmonary cases the temperature is usually normal or subnormal.

One symptom of diagnostic importance which has been reported in a number of the published cases is that of the appearance of small petechial hemorrhages scattered over the skin of the chest, back and arms.

Heart symptoms. Whether the case be of the pulmonary or the cerebral type, heart symptoms often play an important part in the clinical picture. These symptoms, however, are of such a general character that it is usually impossible to say whether they are caused by the direct involvement of the heart itself in the embolic process or whether they are due merely to the grave involvement of the other organs. The heart action is often rapid and feeble; dyspnea and cyanosis are common features; sometimes there may be precordial oppression or distress or indefinite epigastric or chest pain, but of attacks of characteristic anginal pain I have been able to find not a single example in all the large casuistical literature. The reasons for this absence of symptoms characteristic of coronary occlusion will become clear, I think, when the morbid anatomy is considered.

Pathological features. The entrance into the venous circulation of fat droplets or even of small fragments of fatty tissue is easy to understand in the case of bone injuries, in which the torn walls of the venous channels are held widely open. It is much more difficult to comprehend the exact mechanism of such emboli from tissues other than that of bone. In any event, it is evident that the fat reaches the lungs in the form of droplets which are distributed very widely through the small branches of the pulmonary artery and the pulmonary capillaries. In many such arterioles and capillaries the fat takes the form of elongated cylindrical masses, as though these had been built up by a more or less continuous supply of fresh droplets. Around these emboli are found such secondary changes as minute hemorrhages, edema and emphysema. Hemorrhagic infarctions of macroscopic size are not found.

If the patient survives the first few days of the embolic attack the fat gradually disappears from the lung capillaries, so that after a few weeks no trace of fat remains and the lung tissue has regained its normal appearance. The complicated mechanism involved in the disappearance of the fat includes saponification, from contact with the alkaline blood serum, emulsification, and action by the tissue cells.

From the fact that only very small fat droplets can find their way through the pulmonary capillaries it is obvious that the lesions in the other viscera should be of minute size. In the brain the characteristic lesions are small hemorrhagic areas scattered widely throughout the white and grey matter and the pia-arachnoid and representing minute emboli. The kidneys

usually show no noticeable gross changes, but microscopically the appearance is characteristic and striking. There is widespread filling of the vessels of the glomerular tufts with fat and often the larger vasa efferentia are plugged with fat. The remaining capillaries of the kidney contain very little fat and the cellular structure is not damaged. Fat is sometimes, but not always, found in the urine.

In a good many of the early recorded cases a careful examination of the heart was not made, but it is evident from many reports that when any considerable amount of fat reaches the general circulation the heart is regularly the seat of scattered embolic lesions, which may at times be very abundant. Beneath the endocardium of the ventricles, sometimes beneath the epicardium, and scattered through the muscle of the ventricles, are to be seen small, yellowish areas, many of which show a tiny, central red spot. These yellowish spots are seen, microscopically, to be composed of muscle fibers undergoing degeneration and lying in close relation to a small vessel plugged with fat. Such areas of fatty degeneration may develop with surprising rapidity. In a case reported by Colley (8), death occurred from fat embolism 14 hours after the forcible manipulation of an ankylosed knee joint (*brisement forcé*). At the autopsy the characteristic small yellowish spots were seen scattered through the heart muscle and the microscopic examination showed that in these areas fatty degeneration of the muscle fibers was well advanced.

I have been unable to find a single authentic instance of cardiac infarction of macroscopic size in the whole literature upon fat embolism. One case, cited by Colley (8), from the records of the Pathological Institute of Marburg, deserves to be quoted in this connection although its significance is doubtful.

CASE REPORT

A boy of fourteen years was admitted to the Surgical Clinic three days after having sustained a compound fracture of the right leg. Little or nothing was known about his symptoms during this three-day period. Suppuration ensued and a number of bone fragments were discharged, but the wound finally healed satisfactorily and the boy seemed fully convalescent. He had no fever and had shown no signs of cardiac or pulse disturbance. Eight weeks after the accident he died very suddenly. At the autopsy the heart was found to be of about normal size, with some dilatation of the left ventricle. The muscle was of reddish brown color. Section through the interventricular septum revealed in the lower part a "thalergrösse" pale reddish, mottled area of softened, edematous muscle, with areas of less pronounced change in other portions of the ventricular muscle. The presumption that an embolus of some sort would be found in a coronary artery was not realized. Careful search of all the coronary branches failed to show any sort of obstruction, nor were fat emboli found in any of the other organs. Microscopically, the softened area of muscle showed advanced degeneration and much early granulation tissue. The lesions were thought to be several weeks old. In the absence of any other satisfactory explanation, Marchand, who performed the autopsy, was inclined to feel that the lesions might have been caused by fat emboli which subsequently disappeared.

SUMMARY

It is evident that in many if not most cases of fat embolism sufficiently severe to be of clinical significance the heart is involved in the embolic process and may play a part in the fatal issue when this occurs. It is doubtful, however, if such heart involvement ever gives rise to symptoms which are sufficiently characteristic to make the clinical diagnosis possible. The large literature on the subject contains no instances of fat embolism which have presented the classical picture of acute coronary occlusion, nor have postmortem studies ever disclosed an authentic example of myocardial infarction as the result of such embolism.

It is conceivable of course that some fragment of fatty tissue larger than the fat droplets might reach the left side of the heart through a patent foramen ovale (paradoxical embolus) and so result in coronary embolism, but no such happening is recorded and such a possibility is too remote to deserve clinical consideration.

The answer, then, to the question posed in the beginning is that there is no support for the view that fat embolism may at times present the clinical picture of coronary occlusion.

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The following articles, among others, present good reviews of the general subject of fat embolism:

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QUANTITATIVE FORMULATION OF MAXIMUM URINARY SPECIFIC GRAVITY

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Inability to concentrate urine has been known to point to the presence of renal disease since the time of Bright. Measurement of urinary specific gravity is therefore a clinical test enriched and hallowed by more than a century's usage. However, if the significance of hyposthenuria has been empirically recognized, the mechanism by which it is established has been variously and, often, erroneously explained. The almost meaningless routine determination of urinary specific gravity in specimens casually collected is being replaced by techniques of measuring concentrating power under rigid control of hydration. But even with such safeguards, determination of concentrating power is only a semi-quantitative index of renal efficiency and, therefore, to some degree unconvincing and uninforming. The purpose of the present paper is to suggest a quantitative formulation of concentrating power with respect to the kind and degree of renal damage in patients suffering from hypertension.

The formation of urine from glomerular filtrate is dependent upon reabsorption of nearly all the water and much of the dissolved solids of glomerular filtrate. The factors which enter into the formation and concentration of urine have been reviewed by Smith (1937). Of particular interest with regard to the mechanism of hyposthenuria is the evidence obtained by Shannon (1938) and Chasis and Smith (1938) of the existence of two stages in the formation of urine by reabsorption of water. The first phase is "obligatory" and constant in the normal kidney and results in the reabsorption of some 80 per cent of the water of glomerular filtrate in the proximal convoluted tubules and loop of Henle. The second "facultative" phase is variable and subject to the alterations of physiological demands on the functional capacity of the proximal convoluted tubules. Hyposthenuria, since it is due to failure of reabsorption in response to demand, is an expression of decreased efficiency in facultative reabsorption. A further advance towards renal inefficiency results in the familiar fixation of urinary specific gravity of isosthenuria.

This brief consideration of the mechanism of hyposthenuria leads to the view that it is an expression of renal tubular inefficiency. The decrease in efficiency may be extra-renal in origin, as in the failure of reabsorption characteristic of diabetes insipidus which is due to lack of stimulation of

tubular cells by posterior hypophyseal hormone. The impairment of function is more commonly of renal origin, and in this case may be either absolute, i.e., due to loss of tubular tissue, or relative and due to an excess of filtration rate over normal tubular capacity. The intermingling of renal and extra-renal, absolute and relative failure in hyposthenuria is evident from the observation of loss of tubular secretory capacity in diabetes insipidus in hypophysectomized dogs (White and Heinbecker, 1940). A similar blending of factors is evident in the diuresis which follows injections of renin (Pickering and Prinzmetal, 1940). Renin causes a relative increase of filtration rate and renal ischemia, both the results of efferent arteriolar constriction (Corcoran and Page, 1939). Ischemia acts by causing an absolute reduction of tubular capacity, while efferent constriction establishes a relative impairment of reabsorption by increasing the proportionate volume of filtrate. This phenomenon is of significance in the consideration of hypertension because of the similarity of renal hemodynamic changes of hypertension to those which are elicited by the infusion of renin or angiotonin (Corcoran and Page, 1941). Hyposthenuria in hypertension may, therefore, *a priori* be assumed to depend upon absolute and relative failure of reabsorption, the results respectively of renal ischemia and of overloading the deficient tubules by a disproportionately large rate of glomerular filtration.

METHODS

1. *Urea clearance and concentrating power.* Determinations of urea clearance (Möller, McIntosh and Van Slyke, 1928) and maximum urinary non-protein specific gravity (Addis and Shevky, 1922) were made in 72 patients suffering from essential hypertension whose urea clearances were greater than 50 per cent of normal. The measurement of specific gravity was by the method described by Alving and Van Slyke (1934).

2. *Concentrating power, filtration rate and functioning tubular mass.* Determinations of inulin clearance (glomerular filtration rate) and maximum tubular capacity for secretion of diodrast (functioning tubular secretory mass, Tm_D) (Smith, Goldring and Chasis, 1938) were made in 31 patients suffering from essential and malignant hypertension. Both values were corrected to 1.73 square meters of body surface area. Concentrating power was determined within a few days of the measurement of tubular mass and filtration rate.

3. *Concentrating power, urea clearance and functioning tubular mass.* Urea clearance was measured a short time before or after the measurements mentioned in section 2.

RESULTS

1. *Urea clearance and concentrating power.* Inspection of Chart I establishes that, in hypertension, urea clearance tends to remain within normal

limits while concentrating power is usually impaired. Urea clearance was within normal limits in 50 of the patients studied (69 per cent) while concentrating power was normal in only 22 patients (30 per cent). Two patients whose urea clearances were abnormally low had retained the ability to form urine of high specific gravity.

2. *Concentrating power, filtration rate and functioning tubular mass.* The capacity to excrete diodrast by secretion is a measure of the amount of functioning tubular secretory tissue. This value (Tm_D in milligrams per 1.73 square meters body surface per minute) was plotted graphically with

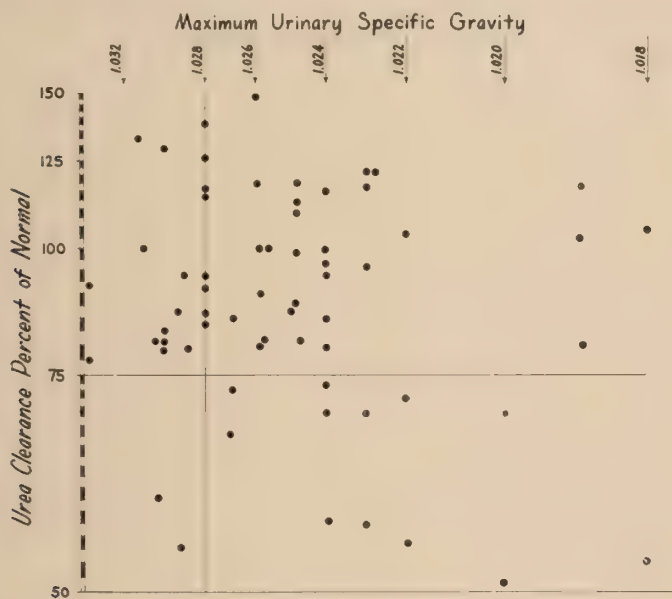


CHART I. Relative maintenance of urea clearance and earlier depression of maximum urinary specific gravity in 72 patients suffering from essential hypertension. Both ordinate (percentage of normal urea clearance) and abscissa (maximum urinary specific gravity) are charted logarithmically. The vertical and horizontal lines indicate the respective limits of normal variation of concentrating power and urea clearance.

reference to concentrating power (Chart II). It is evident from the chart that tubular mass and concentrating power are proportionately impaired functions in patients suffering from hypertension.

It would also be expected that the relative volume of glomerular filtrate presented each unit of tubular mass would be a second variable in the function of concentration. Thus, a grossly inadequate tubule with a normal or somewhat depressed volume of filtrate, or an adequate tubule with an excessive volume of filtrate would be expected to form dilute urine. Scatter diagrams were, therefore, constructed correlating maximum urinary specific gravity directly with tubular mass (Tm_D) and inversely with the

ratio of filtration rate to tubular mass (IC/Tm_D) where IC = inulin clearance in cubic centimeters per 1.73 square meters per minute. If Sp.Gr. be taken as urinary specific gravity, the formulation would be:

$$1) \text{ Sp.Gr. proportional to } \frac{Tm_D}{IC/Tm_D} = Tm_D^2/IC \quad \text{or to} \quad \frac{Tm_D}{\sqrt{IC}}$$

where Sp.Gr. is the value of the significant numerals of the measurement of specific gravity (3rd, 4th, and 5th decimal places).

The scatter of data from the calculation $\text{Sp.Gr.} = Tm_D/\sqrt{IC}$ is shown in Chart III, from which it is evident that the correlation of concentrating power with tubular mass is improved by insertion of the factor of relative volume of filtrate.

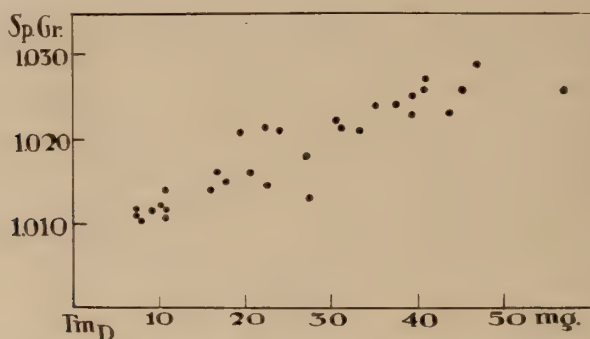


CHART II. The relation of concentrating power to functional tubular mass. Abcissa: maximum capacity for renal secretion of diodrast (tubular mass, Tm_D) in mg. per 1.73 square meters body surface per minute. Ordinate: maximum urinary specific gravity. Both measurements made within a short time of each other in 31 patients with hypertension.

Calculation from the data by the method of least squares¹ establishes the empirical equation:

$$2) \text{ Sp.Gr.} = 3.4 - 5.4 Tm_D/\sqrt{IC}$$

The straight line drawn through the data of Chart III is calculated from this equation. It is evident from this formulation that concentrating power, at least empirically, depends directly upon the amount of tubular tissue and varies inversely with the volume of filtrate poured into the units of tubular tissue.

3. *Concentrating power, urea clearance and tubular mass.* The measurement of urea clearance has, because of its simplicity and significance, become a common test of renal function in clinical practice and is frequently combined with the measurement of concentrating power as a routine in

¹ The authors are indebted to Mr. Brown Robbins, Lilly Research Laboratory, Indianapolis, for this calculation.

the estimation of renal damage. Urea clearance as usually determined (in the absence of extreme diuresis, oliguria or severe renal disease) is equivalent to about 0.6 of inulin clearance, or, expressed as per cent of normal to 0.8 of inulin clearance. On the assumption that this relationship of urea clearance to filtration rate will hold in most cases, the term $UC \cdot 0.8$

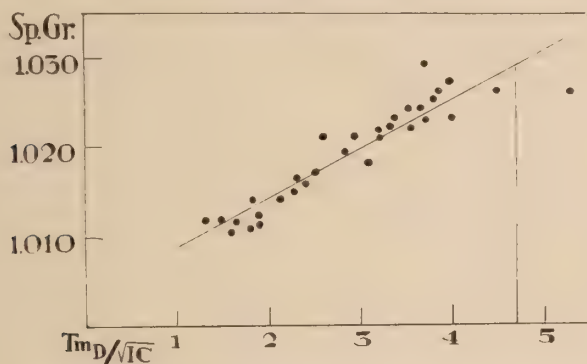


CHART III. Graphic expression of a formulation of maximum concentrating power in relation to tubular mass (Tm_D) and square root of inulin clearance (\sqrt{IC}). Abcissa: Tm_D/\sqrt{IC} calculated from Tm_D in mg. and IC in cc. both corrected to 1.73 square meters body surface per minute. Ordinate: maximum urinary specific gravity. The line drawn through the data is calculated from equation 2. The vertical line is calculated from mean normal values of Tm_D and IC in adult males.

may be substituted for IC in equation 2, where UC is urea clearance in per cent of normal. The equation thus becomes:

$$3) Tm = \frac{Sp.Gr. - 3.4}{5.4} \sqrt{\frac{UC}{0.8}}$$

or

$$4) Tm = \frac{Sp.Gr. - 3.4}{4.8} \sqrt{UC}$$

Using equation 4 and the urea clearances observed in the patients studied in section 2, Tm_D was predicted. The correlation of the predicted values with those actually found is shown in Chart IV, from which it may be seen that the measurement of concentrating power and urea clearance provides the means of calculating tubular mass with an error not usually exceeding 20 per cent. Further, if 53 mg. diodrast-iodine per 1.73 square meters per minute be accepted as equivalent to normal tubular secretory mass (Goldring, Ranges, Chasis, and Smith, 1941) the equation may be corrected for the expression of predicted tubular mass in terms of percentage of mean normal expressed as T . The equation thus expressed is:

$$5) T = \frac{Sp.Gr. - 3.4}{2.58} \sqrt{UC}$$

Accepting the standard deviation of Tm_D as 9.1 mg. diodrast-iodine, the usual limits of normal variation of T (1 times S. D.) become ± 17 per cent.

It should be noted that the mean normal value of Tm_D taken as the basis of this calculation is that of normal adult males, and that the mean Tm_D of normal adult females is about 12 per cent lower.

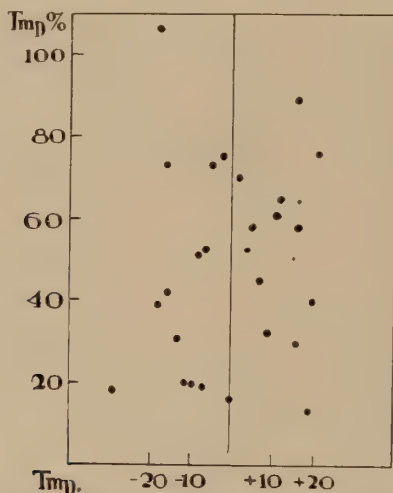


CHART IV. Deviation of predicted from observed Tm_D at various levels of abnormal depression of tubular secretory mass expressed as percentage of normal (T). Abcissa: Percentile ratio of observed Tm_D to Tm_D predicted from the urea clearance and maximum urinary specific gravity, equation 4. Ordinate: Observed Tm_D as percentage of mean normal value.

DISCUSSION

1. *Urea clearance and concentrating power in hypertension.* The failure of urea clearance to decrease to abnormally low values in hypertensives whose loss of concentrating power is evidence of renal disease emphasizes, from a clinical point of view, the value of concentration tests in this condition. The origin of this disparity in the tests lies in the renal hemodynamic changes characteristic of hypertension, viz., efferent arteriolar constriction, increased intraglomerular pressure and increased extraction of water and urea from a frequently diminished volume of plasma (Smith, 1939). The clearance of urea may, therefore, be entirely normal in the presence of a 30 to 40 per cent reduction of renal blood flow. Measurements of tubular mass and filtration rate in hypertensives usually show some reduction of tubular mass and, since filtration rate is maintained abnormally by efferent constriction, there is frequently an abnormally large volume of filtrate poured into each unit of tubular mass. Both terms of equation 1 are, therefore, fulfilled in the direction of a reduction of specific gravity in the concentration test.

2. *Concentrating power, filtration rate and functioning tubular mass.*

Various concepts of the mechanism of hyposthenuria have been reviewed by Fishberg (1939) who concludes that the following factors are important: (a) reduction in number of functioning nephrons, (b) damage to tubular epithelia, (c) decrease in renal blood flow with increase in the relative number of functioning glomeruli. Although the significance of the last factor is questionable in view of the apparent absence of glomerular intermittence in mammals (Smith, 1937, White, 1939), if the concept is rephrased to express variations in relative volume of glomerular filtrate, it is apparent that this formulation is, in a general way, identical with that expressed in equation 2.

A concentrating power of less than 1.010 is only very rarely observed in practice and, in accordance with this observation, it will be noted that the line drawn through the data of Chart III does not extrapolate to values less than 1.010. In this connection it should be noted that a hypothetical concentrating power of 1.007 would, from equation 2 imply values of Tm_D and IC respectively of about 2 mg. and 5 cc., i.e., values which in our experience are inconsistent with life. It should also be noted that the mean normal values of Tm_D and IC (Goldring, Chasis, Ranges, and Smith, 1940) yield from equation (2) a concentrating power of 1.028, a value within the accepted range of normal and only slightly less than that usually observed (1.030 to 1.032).

A recent experimental study of the mechanism of hyposthenuria in dogs (Hayman, Shumway, Dumke and Miller, 1939) cites, as causes of hyposthenuria, partial nephrectomy, tubular poisoning (uranium), tubular degeneration resulting from back pressure, or back pressure with ischemia and demonstrates its temporary occurrence after interference with the renal nerves, during administration of low protein diets and, possibly, in pregnancy. It will be noted that loss of tubular tissue occurs in nephrectomy, poisoning or back pressure, a fact which accords with the data in Chart II. In addition, it is shown that dogs subjected to subtotal nephrectomy and thus made hyposthenuric may, under certain conditions, such as increased concentration of blood colloid (injection of acacia), low blood pressure or injections of sodium sulfate after water deprivation, excrete concentrated urine. These observations are advanced as evidence against a direct relation of tubular tissue mass to concentrating power. However, it would be expected that increased plasma colloid content would increase concentrating power in hyposthenuria, since it reduces the osmotic gradient against which the deficient tubular mass must work and thus alters the normal relationship of tubular mass and concentrating power. Similarly, reduction of blood pressure and, presumably, of the rate of glomerular filtration, reduces the load on the deficient tubules and thus alters the relationship in accordance with the terms of equation 1. The injection of sodium sulphate during water deprivation provides, as glycosuria, a special case in which there may be abnormal interference with the "obligatory"

reabsorption of the proximal tubules. Thus, a hypertensive patient suffering also from renal glycosuria studied by us had Tm_D 43 mg. (corrected for surface area) and inulin clearance 117 cc. per minute. Her apparent concentrating power was 1.040 and the non-glucose urinary specific gravity 1.020. Neither value of specific gravity accords with the terms of equation 2 which would yield 1.025. It may, therefore, be concluded that the normal relationships of concentrating power, filtration rate and Tm_D do not obtain in this condition, nor, in all probability in such states as may be induced by injection of sucrose, sulphates etc., during water deprivation. The temporary hyposthenuria which may follow renal denervation would provide a special case of unusual interest were it not for the possibility that it may express the transient tubular damage due to operative trauma. The hyposthenuria of low protein diets had been variously attributed to decreased renal blood flow and decreased filtration rate. Decreased filtration rate should, however, increase concentrating power. The specific gravity of urine is in large measure determined by its content of urea, phosphates, sulphates and sodium chloride. The intake of these substances is decreased during the administration of low protein diets and their excretion correspondingly diminished. There is, therefore, a decreased stimulation of the activity of renal tubular cells.

It is apparent that other factors than tubular mass and relative filtration rate operate in the maintenance of concentrating power. However, neither highly protein-deficient diets, increased concentration of blood colloids nor glycosuria or exogenous sulphaturia frequently complicate the measurement of concentrating power in clinical practice, so that the relationship expressed in equation 1 may be considered as valid in most circumstances.

3. *Concentrating power, urea clearance and functioning tubular mass.* The relationship of concentrating power, urea clearance and tubular mass predicted from equations 4 and 5 to observed tubular mass is such that the use of equation 5 as an index of the integrity of renal tissue seems sufficiently accurate for many clinical purposes. The chief criticism of the measurement of concentrating power in clinical practice is that it offers a qualitative rather than quantitative measure and thus that "for measuring the extent of renal damage . . . (it) is not suited" (Alving and Van Slyke, 1934). The combined measurement of concentrating power and urea clearance² and calculation of percentage normal tubular mass from equation 5 seems to remove this objection to the use of concentration tests. It is, of course, clear that such a prediction can only be made with due reference to the conditions of measurements of both concentration power and urea clearance. The use of equation 5 is, therefore, proposed

² By combined measurement is not meant that the tests are done within the same day. The usual practice is to measure urea clearance on one day and start the concentration test on the next.

as a means of assessing renal structural integrity in hypertension until such time as the measurement of tubular mass by more direct means becomes generally feasible.

4. *Application of this formulation to other types of renal disease.* Acute Bright's disease is mimicked in many respects in the course of experimental nephrotoxic nephritis in dogs, notably in relative decrease of glomerular filtration due to inflammatory changes in the glomeruli shown to occur in the experimental disease (Fouts, Corcoran and Page, 1941). A similar functional disturbance characterizes pre-eclamptic and eclamptic toxemia of pregnancy in human beings (Corcoran and Page, 1941). As would be expected, patients suffering from acute Bright's disease and toxemia of pregnancy usually excrete small volumes of highly concentrated urine, and the relation of renal hemodynamic and tissue changes to concentrating power are those which would be predicted from equation 1. Similarly, in chronic Bright's disease reduction of concentrating power roughly parallels that reduction of urea clearance (Alving and Van Slyke, 1934), since in this condition whole nephrons are destroyed together, and the degree of disturbance of glomeruli and tubules is more nearly equal than is the case in hypertension. It is, therefore, not improbable that concentrating power varies directly with tubular mass and inversely with the square root of the rate of glomerular filtration in other renal diseases than hypertension. An examination of this possibility must form the subject of a subsequent report, since the data at present at hand are inadequate.

SUMMARY

1. Estimation of urinary concentrating power is much more sensitive than the determination of urea clearance in the demonstration of renal damage in hypertension. This characteristic of the renal function in hypertension is the necessary consequence of the renal hemodynamic changes which occur in this disease.

2. The maximum ability of the kidney in hypertension to concentrate urine is shown to be proportional to the functional tubular secretory mass (Tm_D) and inversely proportional to the square root of the rate of glomerular filtration. This relationship may be expressed in the equation

$$Sp.Gr. = 3.4 - 5.4 Tm_D \sqrt{IC}$$

where Sp.Gr. indicates the third and fourth decimal places in the measurement of maximum urinary specific gravity, Tm_D the maximum capacity for excretion of diodrast in milligrams per minute and IC inulin clearance in cubic centimeters per minute. Both inulin clearance and Tm_D are expressed in units per 1.73 square meters of surface area.

3. From this equation and from the normal values of Tm_D and IC and the usual relationship of the clearances of inulin and urea an equation is

derived by which an approximate calculation of functional tubular mass may be made from the equation

$$\frac{\text{Sp.Gr.} - 3.4}{2.58} \sqrt{UC} = T \text{ per cent}$$

where UC is urea clearance in per cent of normal and T the approximate percentage of normally functioning tubular tissue. There is thus established a clinically useful quantitative application of the measurement of maximum urinary non-protein specific gravity.

4. General considerations suggest that this formulation will apply in other conditions than hypertension.

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THE DIAGNOSIS OF ANEURYSM OF THE HEART

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The first description of aneurysm of the heart has been attributed to Galaeti (1) in 1757. However, the first detailed account of the condition was by Baillie (2) in 1793. Since that time various papers have appeared dealing with the condition. It is unnecessary to review the complete literature as excellent reviews have appeared from time to time, such as those of Hall (3), Sternberg (4), and Parkinson, Bedford and Thomson (5). The majority of the reports have dealt with post-mortem descriptions and it is only recently that the ante-mortem diagnosis has been made with greater frequency. In 1926 Pletnew (6), in a summary of three hundred cases previously described, stated that a correct diagnosis had been made ante-mortem only six times. Since x-ray has come to play a greater part in cardiology, the diagnosis has been correctly ascertained much more often. Nevertheless, it is still in many instances a difficult diagnosis to make with assurance. It, therefore, seems worthwhile to critically analyze the criteria on which the diagnosis may be based and to describe those signs which proved most valuable in a series of thirteen patients, nine being followed to autopsy, who have been in Kings County and Long Island College Hospitals.

In the pathological descriptions of earlier years the incidence of the condition was very low as compared to more recent studies of autopsy material which have been made. Parkinson, Bedford and Thomson (5), combining their own statistics with those of other authors, reporting its occurrence following coronary occlusion, state that the incidence is 9 per cent. Even if one were to assume that there has been an increase in coronary occlusion which is not proven, as before the classical description by Herrick (7), the condition was usually unrecognized, it would seem that there must be some reason for the discrepancy. The most probable explanation is that the earlier authors considered as aneurysm only those cases in which there was a very definite bulging of the ventricle beyond the general contour of the heart, whereas recently less distinct lesions have been included. In some reports small indentations of the wall in the region of an old infarct, even when it does not affect the epicardial surface, have been considered as aneurysms. This seems hardly warranted; otherwise, one could decide that in most instances where an area of myomalacia takes place an aneurysm exists. Gubner and Crawford (8), by roent-

genkymography, showed that in a large percentage of cases of coronary occlusion, systolic expansion of the infarcted area took place. Similar results were obtained on fluoroscopy by Master and his co-workers (9). It seems doubtful if a small lesion such as this warrants the description "cardiac aneurysm" and it would seem better to confine the term to such as show a permanent, localized bulging or during systole, a well-marked localized expansion beyond the contour of the rest of the heart. One sees instances of the latter in which, on fluoroscopy, there is a localized ballooning of the wall in systole which during diastole collapses so that the heart wall appears flattened. It might be possible to see a bulge in the latter if the picture happened to be taken at just the height of systolic contraction.



FIG. 1



FIG. 2

FIG. 1. Aneurysmal bulge at upper part of the left border of the heart. The aneurysm was confirmed by x-ray and autopsy examination.

FIG. 2. Angulation of left border of the heart. The aneurysm was proven by x-ray and autopsy examination to be in the lower part of the anterior wall of the left ventricle and the apex, the flattened area.

This was the type of case reported by Christian and Frik (10) in which, although the diagnosis was correctly made by x-ray examination, the aneurysm was incorrectly located as the normal part of the heart was considered to be the aneurysm. Figure 1 illustrates a permanent, localized bulging and figure 2, the second condition described.

Aneurysm of the ventricular septum is a condition which is only diagnosed post mortem. It is possible that such an aneurysm might produce the Bernheim syndrome or if very extensive, enlargement of the heart to the right on x-ray examination may be seen. However, there are so many conditions which cause the latter frequently, that the correct diagnosis is unlikely to be made. Our main concern, therefore, is with the findings which enable one to diagnose aneurysm of the walls of the ventricles.

History: The vast majority of aneurysms of the ventricular wall are the aftermath of coronary occlusion and occlusion of the anterior descending branch of the left coronary artery seems to be followed by aneurysm more often than occlusion of other vessels in the heart. A history of a preceding coronary occlusion is thus of great value in supporting the diagnosis of aneurysm when such is suspected. Fulton (11) states that recurrent pain, lasting for hours or days, after coronary occlusion, suggests the possibility of an aneurysm. This was not seen in our series. Some complained of typical angina pectoris but others had no pain following the occlusion. A feature in some of these cases was the early onset of heart failure following recovery from the occlusion. This seems logical as in order to develop the type of lesion which we included a fairly large area of myocardium had to be involved, thus considerably reducing the functional capacity of the heart. This was, however, not constant and it was surprising how much some of these individuals were able to accomplish with such serious cardiac pathology. Trauma to the heart is a rare cause of aneurysm as is its appearance as a result of congenital defects. Syphilitic, rheumatic and mycotic aneurysms have been described but are very rare.

Physical signs: The most important physical finding is the appearance of abnormal pulsation in the precordium. The apex pulsation may be displaced outward, more diffuse than normal and both forceful and heaving. This is, however, often seen in large hearts without aneurysm and would only supply some confirmation if an aneurysm were being considered as a result of other evidence. In many cases the diagnosis can be made with almost certainty through the appearance of a pulsation in the precordium which is separate and distinct from the apex beat. This is particularly true when the abnormal pulsation is situated above the fifth rib. Libman and Sacks (12), Libman (13) and Dressler and Pfeiffer (14) have stressed the value of this sign. It was the most pathognomonic physical finding in our series. Sometimes the abnormal pulsation appeared before and lasted longer than the apical thrust. A sign which has been stressed by many authors is a muffling of the heart sounds and a disproportion between the intensity of the sounds and the forcefulness of the pulsation. This was not conspicuous in our cases. Some had heart sounds of normal intensity while in others they were faint. Many, but not all, of those who showed a weakness of the heart sounds were in heart failure at the time; hence, such might be expected without aneurysm. Gallop rhythm was not noticed in any of our cases. It would likewise be evidence of myocardial failure and not particularly characteristic of aneurysm. Murmurs do not appear to be of any particular help in the diagnosis although a systolic murmur is frequently present. Percussion is only of value in a very large aneurysm and is much inferior to x-ray study. Lutembacker (15) stressed the value of pain over the apex but this was not present in our patients and is of doubtful value.

Electrocardiography: This is useful only when it confirms the presence of a previous coronary occlusion. There is no pattern characteristic of aneurysm of the heart.

X-ray examination: The introduction of radiological examination in cardiac diagnosis marked the advent of greater accuracy in determining aneurysm of the heart. It is, however, still difficult and many times one cannot be positive. The first case diagnosed by x-ray examination was described in 1922 by Sézary and Alibert (16). Fluoroscopy in all positions should be done as this yields the most important information. Not only can one study the cardiac contour but the pulsations as well. Films should be taken, not only in the postero-anterior position, but in oblique views also, the best position being determined by fluoroscopy. Certain aneurysms of the anterior wall and aneurysms of the posterior wall can be seen only in the oblique positions. Roentgenkymography yields information as to the contractions and may accurately diagnose the site of the aneurysm when one is in doubt as to which part of the contour represents the normal muscle and which the aneurysm. It confirms the impression of the pulsations gathered on fluoroscopy. Studies after diodrast injection may clearly demonstrate the aneurysm if it is not filled with thrombus.

Parkinson, Bedford and Thomson (5) state that the x-ray diagnosis depends on the following findings: 1) Enlargement of the left ventricle with deformity of its contour. 2) A localized protuberance inseparable from the heart shadow on rotation of the patient. 3) Abnormal or absent pulsation of the aneurysmal zone. 4) Evidence of adhesions between the heart and the chest wall or diaphragm. 5) Calcification of the wall of the sac or of its contained clot.

In aneurysm of the left ventricle these authors lay great stress on an abrupt ledging on the anterior contour of the heart as seen in the right oblique position.

Aneurysms of the posterior wall, best seen in the left oblique position, frequently cause displacement of the esophagus.

Undoubtedly changes in the contour of the heart are of the greatest importance in drawing attention to the diagnosis. Unfortunately, however, the most common site of aneurysm, the apex, is the position in which it is least readily recognized. This region of the heart mingles with the diaphragmatic shadow and this tends to obscure any bulging. A diffuse eccentric apex rounding or a broadened and blunted apex have been described as characteristic. It is very difficult often to differentiate this, however, from the type of heart seen in hypertension and aortic insufficiency. As Zdansky (17) points out, aneurysms must reach a considerable size to show clearly circumscribed outbulging at the apex. The visualization of the changes at the apex may be greatly aided by study during very deep inspiration or by inflating the stomach with gas. Aneu-

rysms higher in the anterior wall and in the posterior wall, which are usually basal, can be more readily visualized. In our series the lesion was recognized by the abnormal contour of the heart in about 65 per cent of the cases.

Abnormal pulsations are frequently of the greatest value in the recognition of the condition. This can be seen on fluoroscopy and studied in detail by roentgenkymography. They may vary from systolic expansion to absent pulsation. Sometimes, as in one of our cases, a most striking ballooning of the aneurysm takes place during systolic contraction. Schwedel and Gross (18) state that the pulsations in their cases were either synchronous, asynchronous, systolic or contrapulsile. In none of the cases which we studied were the pulsations of normal character. The reason why every case does not present expansile pulsation is that this may be prevented by thrombus in the interior, by calcification of the wall or by marked thickening of pericardial adhesions.

Evidence of localized pericardial adhesions is an important sign. In none of our cases was this seen during life but the pericardium was found to be adherent to the aneurysm in almost all on which a post-mortem examination was performed. Gross and Schwedel (19) have stressed the value of this finding and also mention increased density of the heart shadow in the region of the bulge as important.

Calcification of the wall of the sac or of its contained clot when present are obviously valuable. It was not seen in our cases. Care must be taken to differentiate this from calcification of the pericardium. To be certain the calcification should not be confined to the surface and it must be localized. Calcification of the pericardium is on the surface and is usually more widespread.

DIFFERENTIAL DIAGNOSIS

Tumor of the heart is probably the most difficult to differentiate from aneurysm of the heart as it may cause a definite localized hump on the cardiac contour. In this condition the history of a previous coronary occlusion is usually absent and there may be evidence of carcinoma elsewhere, the tumor being metastatic. The pulsation in solid tumors is synchronous with the heart beat, while in aneurysm there is usually systolic expansion to absent pulsation. In soft tumors, such as very vascular sarcomata or hemangiomata, a reversal of pulsation may take place. Fulton (11) describes a case, which responded well to antiluetic therapy, in which there was systolic expansion. Most frequently in tumor the heart in general is not enlarged, whereas in aneurysm it is almost invariably so.

Aneurysm of a Sinus of Valsalva may project to the left and upward and thus cause difficulty. A positive Wassermann reaction or aortic insufficiency would suggest this as a likely diagnosis.

Aneurysm of a coronary artery is rare and seldom large. If it reaches a sufficient size to be easily seen, it may readily be mistaken for an aneurysm of the heart itself.

Aneurysm of the descending aorta may be seen projecting to the left of the cardiac contour but careful radiological study will easily establish the correct diagnosis.

Diverticulum of the pericardium, loculated pericardial effusion or cyst of the pericardium may resemble aneurysm. Cushing (20) found on a review of the literature that the first in most instances was seen on the right side where aneurysms are not common and also believes that a change in shape of the shadow on respiration is an important diagnostic feature. The history of a previous pericarditis may help in differentiating effusion and the type of pulsation seen in aneurysm may be an aid. Differences in density of the x-ray shadow between the heart and the pericardial disease may at times help to settle the matter.

An enlarged pulmonary conus secondary to mitral stenosis, congenital heart disease, cor pulmonale or Ayerza's disease should give little difficulty as in these the x-ray rarely simulates aneurysm and the clinical features of these diseases are characteristic.

Tumors of the mediastinum or lung can be separated by careful radiological study and the clinical features of pressure in the mediastinum or evidence of pulmonary disease.

The para-apical pad of fat is easily differentiated from an apical aneurysm by x-ray examination.

CONCLUSIONS

1. The signs which are most frequently present and appear to be most important in the diagnosis of aneurysm of the heart are: (a) A history or electrocardiographic proof of previous coronary occlusion. (b) The presence of an abnormal precordial pulsation distinctly separated from the apex pulsation particularly when it is situated above the fifth rib. (c) On x-ray examination a localized bulge which cannot be separated from the heart shadow in any view in which it can be seen or an angulation of the left border of the heart. (d) Systolic expansion in the region of the abnormality as seen on fluoroscopy or roentgenkymography is practically conclusive evidence and small or absent contractions in this area are strongly suggestive. (e) Localized pericardial adhesions or calcification of the aneurysmal wall or its contents are also of value when present.

2. The following conditions simulate aneurysm of the heart most closely and must be carefully differentiated from it: (a) Tumor of the heart. (b) Aneurysm of a Sinus of Valsalva. (c) Aneurysm of a coronary artery. (d) Calcification of the pericardium. (e) Diverticulum of the pericardium. (f) Loculated pericardial effusion. (g) Cyst of the pericardium.

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PERSISTENT AURICULAR PREMATURE SYSTOLES OBSERVED FOR TWENTY-FOUR YEARS

CASE REPORT

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Premature systoles, with special regard to etiology and prognosis have been the subject of many reports (1). Although in the past they were considered as indicating unquestionable heart disease, it is now the consensus that their occurrence is frequent in individuals with normal hearts. Upon analysis as much as fifty per cent of patients with extrasystoles may be found to be free of demonstrable organic heart disease. Furthermore, the occurrence of extrasystoles in patients with organic cardiac disease does not necessarily indicate a grave prognosis. Nor is the type and frequency of premature beats any help in reaching any significant prognostic conclusions. These facts are of particular importance since one is often confronted with a patient presenting numerous extrasystoles and symptoms associated with their occurrence in whom a diagnosis must be established. The following case is, therefore, of particular interest since an unusual occurrence and persistence of auricular premature systoles over a period of twenty-four years has resulted in erroneous diagnoses and undue anxiety by numerous physicians examining the patient.

CASE REPORT

History. The patient, a 53 year old unmarried Jewess, native of Austria first came under observation for "heart disease" in March 1917. At that time, at the age of 29, in the process of a physical examination as a possible tuberculosis contact (a mother and sister having succumbed to this disease), it was noted that her heart was beating with total irregularity. The onset of this condition was vague but had apparently existed for at least nine years before the initial examination. The marked irregularity was proven by the electrocardiogram to be multiple auricular premature systoles superimposed upon a normal sinus rhythm. Clinically the extrasystoles were associated with complaints of constant palpitation and precordial pain. The latter varied from an occasional sharp twinge beneath the left breast to a steady dull-like pain that persisted for several hours. Consciousness of the heart beating was always present. The precordial pain never radiated and was not associated with the usual symptoms of the anginal syndrome such as nausea, eructations or paroxysmal dyspnea. Exertional dyspnea, however, and cough with and without expectoration were persistent complaints.

The past history revealed diphtheria at the age of 3 and 13; migratory joint and muscle pains at 14 years of age; scarlet fever at the age of 15; frequent bouts of

tonsillitis and colds every winter with tonsillectomy performed at the age of 19; and an attack of polyarthritis involving all large joints with symptoms persisting for one week at the age of 26. Menses began at 16 and were regular up to the age of 46. The flow was always profuse and on three occasions necessitated hospitalization for severe hemorrhage. Total climacteric occurred at the age of 52. Symptoms usually associated with the menopausal syndrome were absent. Alcoholic beverages and tobacco were not indulged in, but the patient consumed regularly six to seven cups of coffee and at least two cups of tea daily. Efforts to curtail the habit were futile.

Examinations. From March 1917 to January 1938 the patient was observed at intervals of three weeks to two months in the Cardiac Clinic of the Third Medical Division (New York University), Bellevue Hospital, and subsequently to date in the New York University College Cardiac Clinic. Heart examinations repeatedly

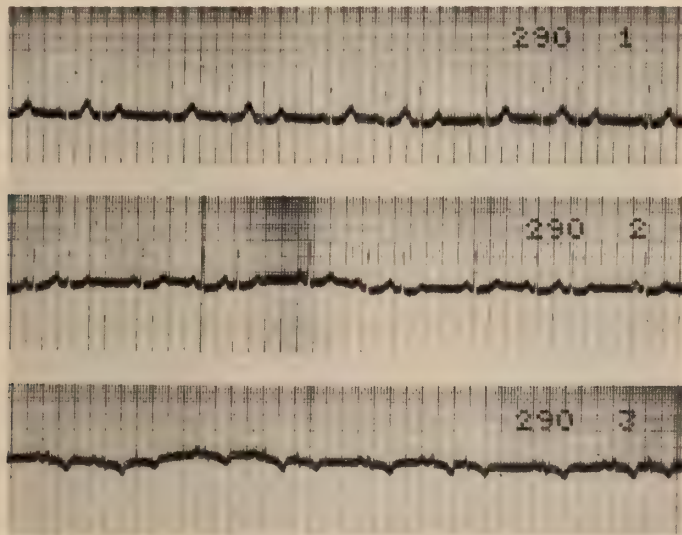


FIG. 1. Electrocardiogram of patient at time premature systoles were first noted. Auricular premature beats occurring every third beat produce a trigeminal rhythm.

revealed a marked irregularity which, on auscultation simulated auricular fibrillation. However, the electrocardiogram (figs. 1, 2, 3) demonstrated numerous auricular premature systoles, occurring singly, in runs of two or three, occasionally in short runs of paroxysmal tachycardia and often in runs of coupling and tripling. The ventricular rate ranged between 60 and 200 beats per minute with a pulse deficit of 5 to 50 beats. In a five minute interval extrasystoles would occur from 5 to 150 times. The heart sounds were good with accentuation of the second sound over the pulmonic area as compared to the aortic area. At times a soft blowing systolic murmur was audible at the apex. A diastolic murmur was never present although during many observations the additional sounds attributed to the premature systole would often simulate a diastolic murmur. The heart was not enlarged. Repeated fluoroscopic examinations and teleoroentgenograms (fig. 4) from 1917 to 1941 revealed a normal size and shape. The maximum transverse diameter averaged 12.2 cm.; the total length 13.3 cm.; aorta 5.2 cm. and the width of the pulmonary fields 23.2 cm. Blood pressures ranged, for the systolic level, between 92 and 140 mm. Hg, and for the

diastolic level, between 50 and 82 mm. Hg. With the exception of very slight edema of the ankles attributed to moderate varicosities of the lower extremities, the rest of the physical examination during the 24 years of observation was essentially negative.

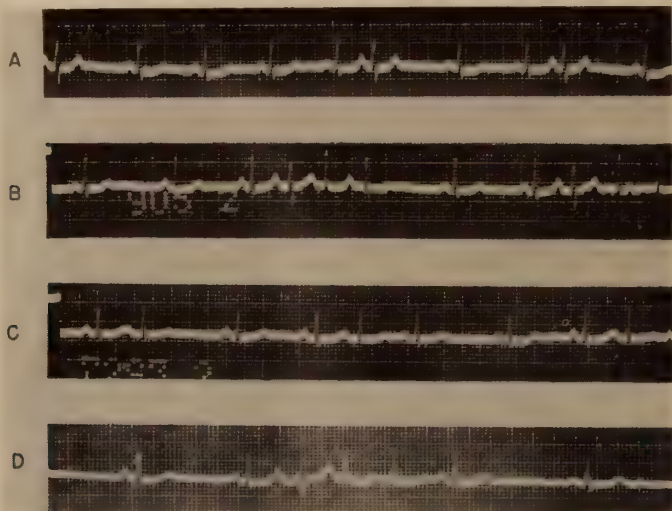


FIG. 2. Representative electrocardiograms (Lead II) over a period of 24 years illustrating type and frequency of auricular premature systoles. A, October 1930; B, November 1931; C, June 1935; D, May 1939.

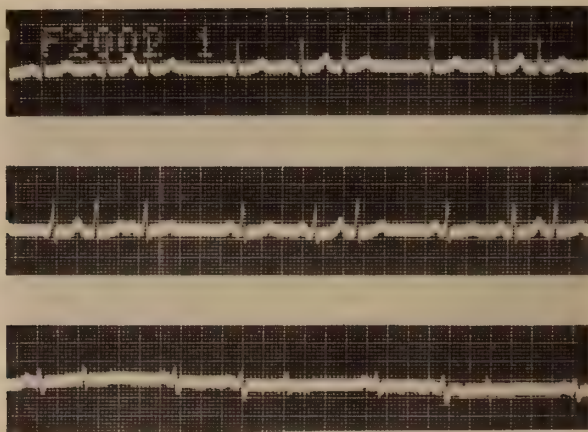


FIG. 3. Electrocardiogram (July 8, 1941) illustrating essentially no change from original tracing (fig. 1).

Laboratory data. Laboratory data consisted of repeatedly negative Wassermann reactions with cholesterol and alcoholic antigens, negative urine examinations and normal blood counts. The red blood count was in the range of 4.0 million cells, with a hemoglobin of about 13 grams. Blood sugar was recorded as 70 mg. per cent. The basal metabolic rate (1937) was minus 5.3 per cent.

Course. Throughout the 24 year period of observation complaints referable to the heart were many, and consisted, in the main of palpitation, precordial pain and shortness of breath on effort. Nevertheless, signs of congestive heart failure were never discernible. At several clinic visits the patient complained of migratory joint pains, but objectively there was no evidence of arthritis or limitation of joint motion. Appendectomy was performed at the age of 33, and an attack of cholelithiasis was noted during August 1938.

Efforts to abolish the arrhythmia were futile. Exercise did not diminish or increase the number of extrasystoles. Digitalis, often in toxic doses, was administered



FIG. 4. Teleroentgenogram showing configuration of heart silhouette after 24 years of observation.

over a period of 12 years without any therapeutic benefit. Several courses of quinine therapy were of no avail. The mainstay of treatment was that of sedation.

COMMENT

Although the occurrence of premature systoles is regarded as a common cardiac arrhythmia, it was surprising to note that the literature is scant in reports referable to long duration of this condition. Mackenzie (2) in his discussion on extrasystoles mentions several patients who presented premature beats of all varieties for over 25 years and one patient who apparently had the arrhythmia for over 50 years. Grassmann (3) noted a woman with premature beats of over 67 years' duration without demonstrable heart disease. A duration of 30 years was noted by Koppang (4), while Smith (1h) mentions a physician who noted the premature beats for

25 years with repeated occurrences upon smoking. Walsh (5) also reported on a physician who presented multiple ventricular premature beats over a period of 40 years. Campbell's (6) case of auricular premature systoles was observed for 12 years, while Boas and Levy (1k) observed a patient with knowledge of extrasystoles for 7 years. All the above cases, as well as our own have one thing in common, i.e., the absence of demonstrable heart disease. Many more such cases must exist, but unless the patient is himself conscious of the occurrence of premature beats, or their presence is noted only during a routine physical examination and the patient subsequently observed for possible serious heart disease, the condition is usually considered of no importance. It is noteworthy that in the above cases, the arrhythmia was noted in two instances by physicians themselves. In some of the reported cases it is difficult to determine the types of premature beat. Whether the premature beats occurred throughout the years mentioned or whether they were noted to occur at the time of the last examination and the duration of the arrhythmia obtained from the patient's history was also obscure. Our case is, therefore, unique in that we have had the opportunity to have the patient under constant observation for 24 years.

We were unable to determine the etiological factor responsible for the arrhythmia. From the history it is quite impossible to indict any one precipitating cause. Diphtheria, scarlet fever, rheumatic fever and excessive use of coffee and tea may have all contributed. The bout of rheumatic fever was particularly disturbing since it led to the patient's frequent observation for active rheumatic heart disease. An important reason for this was the previously held teaching that auricular premature systoles are unusual in normal individuals, that they are usually associated with actual rheumatic carditis and that their persistence foreshadows the development of auricular fibrillation. The concern of physicians examining this patient has been reflected in the patient developing a superimposed anxiety neurosis. This case emphasizes the necessity for care in diagnosing organic heart disease on the basis of premature beats themselves. The responsibility for doing so rests entirely upon the physician. In the words of Mackenzie (2), "It may therefore be stated that when the extra-systole is the only abnormal sign, the prognosis is a favourable one, and where it is associated with other signs the prognosis is to be based upon these other signs."

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A NOTE ON THE INHERITANCE OF CARDIOVASCULAR DISEASE—RESULTS OF LIFE INSURANCE INVESTIGATIONS

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The study of heredity in man is a difficult and intricate task, once one goes beyond the inheritance of simple unit characters. This is particularly true of the investigation of the inheritance of disease which, in most instances, is a composite of many factors or causes, some intrinsic and some obviously environmental. In general, neither adequate data nor adequate techniques have been available to the student of heredity to permit him to unravel the diverse elements which enter the picture. Nevertheless, the literature in this field is extensive. In this paper, we shall attempt only the briefest review of the general literature, summarizing particularly the results of life insurance studies which are generally little known to the rank and file of physicians. Most of these investigations on the longevity of persons either or both of whose parents died of cardiovascular or renal disease, are limited to insured men whose parents died at relatively young ages, usually under 60. We shall also include the preliminary results of a recent study made in our office along similar lines.

General literature. Excellent summaries are available in the medical literature on the inheritance of cardiovascular and renal diseases and of specific related factors such as arteriosclerosis and hypertension. Of especial value are those by Williams, (1) Campbell, (2) Osman (3) and Musser and Barton (4). The complexities and difficulties in such studies in man are admirably stated by Williams and Campbell. This literature, however, centers very largely on striking instances of the spread of these diseases in families, usually two generations only. While such instances are suggestive, they do not necessarily prove the operation of heredity; for, such cases could occur merely as a matter of chance. The best approach for such investigations is to collect selected family records of patients with cardiovascular disease and to compare the incidence of these conditions among relatives with that in properly selected controls. Worthwhile studies of this type are unfortunately few.

The first extensive series in this country is that reported by O'Hare (5) and his associates. In 68 per cent of 300 patients with hypertension,

treated privately or at the Peter Bent Brigham Hospital, they found that one or more members of the patient's family suffered from some cardiovascular or related disease—heart disease, apoplexy, Bright's disease, arteriosclerosis or diabetes mellitus. Among 128 hospital patients of comparable ages, admitted for non-vascular diseases, the corresponding proportion was only 37.5 per cent.

Barach (6) reported the incidence of vascular disease in the families of a sizable group of patients, but without any data on a control group. His study is important because of the differences he obtained between intensively studied cases and those in which the history was obtained in routine fashion. Among the former, nearly 95 per cent of the family histories were positive as compared with approximately 50 per cent in the other and larger group.

Nuzum and Elliot (7) collected and analyzed the family histories of 500 patients with hypertension, age 45 and over, 90 of whom showed renal damage, and of a control group of 250 non-hypertensive hospital patients. In the hypertensive group, positive family histories of vascular disease were only slightly more frequent than in the control group, the percentages of such histories being 30.8 and 29.6 per cent respectively. It is hard to understand why these results are so different from those of other investigators. An important factor may be the care used in history taking, as indicated by Barach's finding. It is notable, however, that in Nuzum and Elliot's series, those with two or more members of the family affected constituted 12.2 per cent of the hypertensive group, but only 7.2 per cent of the control group.

Pearl (8) studied the incidence of cardiovascular-renal diseases among the immediate relatives (parents and siblings) of 285 patients with some form of these diseases and of 362 patients without any such disease. He found that the known frequency of such diseases among the relatives of the first group was about one and one-half times that among relatives of the second group. The facts in the two groups were tabulated separately for living and dead fathers, mothers and siblings, and except as regards fathers deceased at the time of observation, the proportion of relatives with cardiovascular-renal diseases was consistently higher for the patients suffering from such diseases. It is to be noted, however, that the patients with cardiovascular diseases, especially the females, were appreciably older, on the average, than the patients treated for other causes. Consequently, in the former group, the proportion of the deceased relatives was greater. The living relatives were also older and, consequently, more of them had attained ages at which these diseases usually have developed. These facts may account for a good part of the difference between the two groups of patients.

In a recent study by Ciocco, (9) compiled from insurance records, and based upon the parental history, given at the time when the insurance

was issued, of white men dying in 1937-1940 from cerebral hemorrhage, heart and circulatory disease, compared with those dying from other causes, he found that the proportion, both of mothers and fathers dying from the same causes was about one-fifth higher in the former group than in the controls. The differences were particularly marked for men dying after the age of 50.

In Europe, the best work along these lines has been done by Weitz (10) who found that of 82 persons, mostly of peasant stock, with symptoms of hypertension, 93 per cent had one or more relatives (parents and siblings chiefly) with some cardiovascular-renal disease, and in 77 per cent, one or both parents had died of such diseases. In a control series, consisting of 267 non-hypertensives, 45 years old or over, only 30 per cent reported parents dying from cardiovascular-renal diseases. Moreover, these deaths occurred at more advanced ages in the control series, 31 per cent of the parents dying over 70 as compared with 14 per cent in the hypertensive group. Weitz also found that among 93 siblings of his hypertensive cases whom he examined, above-average blood pressures were more frequent than among the control cases, and of the 38 siblings over 55 years of age, 18 had a systolic blood pressure in excess of 150 mm. Hg. On the basis of careful analysis of his data, Weitz concluded that the predisposition to hypertension behaves genetically as a Mendelian dominant character.

The differences in the blood pressures of twins are also of interest in this regard. Von Verschuer (11) found differences greater than 6 mm. Hg. (systolic pressure) in only 37 per cent of 35 pairs of identical twins, as compared with 68 per cent of 22 pairs of fraternal twins. Similarly, in the experience of Curtius and Korkhaus (12) on 42 identical pairs and 25 fraternal pairs, these ratios were 33 per cent and 52 per cent respectively.

Characteristics of insurance data in relation to heredity. Before presenting the results of insurance studies, it will be well to consider certain difficulties inherent in the analysis of family histories from life insurance data. Some of these difficulties apply also to non-insurance data on heredity. In the first place, longevity is not a simple entity but rather a complex of many factors. Cardiovascular disease, furthermore, usually develops in mature life. The period of time involved in developing these conditions is usually so long that the individual is exposed to the risk of dying from any one of a number of other causes, such as violence or infections quite unrelated to the disease group we are considering. The basic records likewise do not permit systematic segregation according to etiological types of cardiovascular disease, either for the insured individual included in these studies, or for the affected numbers of his family. Consequently, these studies do not deal with etiologically "pure" groups, although hypertensive or arteriosclerotic types predominate. Insofar also as insurance studies are concerned with individuals living at first observation, who have either or both parents or one or more siblings dead from cardiovascular disease, they are not dealing with random samples of the population. In that

respect, there is a very definite selection. The problem is further complicated by the factor of the order of birth of the individual, and partly associated with this, the age of the parents, particularly the mother, at the birth of the individual. Effects of environmental conditions on children in broken families must also be considered. And not least among these elements which tend to confuse results in such studies is the long-term upward trend in human longevity which has been especially marked in the past two generations.

In the studies based on insurance material, there is also to be considered the effect of medical selection. Individuals with serious defects applying for insurance are rejected for life insurance, or at least for standard insurance upon which such studies have been made, and such persons would consequently be eliminated from observation. Life insurance physicians have long viewed a poor family history with suspicion and, consequently, the selection of persons presenting such histories would, on the whole, be more rigorous than for other applicants. The insured in these investigations, therefore, are the ones who have not only survived but also those who, in the judgment of the company, are most likely to give a satisfactory mortality experience. Applicants for insurance have long been aware of this viewpoint of the companies' medical officers, and for that and other reasons, misstatement of the age and the cause of death of the deceased parents is fairly common. Finally, knowledge of the causes of death of parents, particularly a generation or more ago was often inaccurate and, consequently, the convenient designations of heart disease, apoplexy and Bright's disease were often incorrectly reported.

On the other hand, life insurance records have certain definite advantages in this type of investigation. Persons accepted for standard insurance form a fairly homogeneous and above-average group with respect to social, occupational and economic status. Observations as to the mortality of the group are accurate and can be carried out over long periods. Information as to the causes of death of the insured individuals is of relatively high quality, especially in recent years. It must be kept in mind, however, that medical concepts with respect to the development of cardiovascular disease have changed enormously during the past 40 years, especially with regard to the role of hypertension. The net result has been to throw much more emphasis on the cardiac manifestations. Consequently deaths from heart disease have formed a rapidly increasing proportion of the total. Because of this, both with respect to parents and offspring, it is desirable to deal with the cardiovascular-renal group as a whole.

Most of the insurance studies have disregarded the causes of death of the insured. This arose largely from the prime interest of the investigators in the total mortality for its practical use in the selection of applicants for life insurance. Consequently, in many instances, this much desired information on the specific mortality from cardiovascular diseases is lacking.

Method of reporting results. Results of these insurance investigations

are presented in the form of ratios of the actual deaths occurring within the period of observation to the number of deaths expected. The figure for the expected or normal is based upon a table of mortality among normal or "standard" risks, which is usually selected as representative of the time period covered by a particular investigation. In these computations, the age of the individual at issue of insurance and the duration of observation are taken into account. The selection of the standard mortality table is extremely important because of the long-term downward trend in death rates and the differences in the extent of the declines at different ages.

Specialized Mortality Investigation (1869-1900). The first extensive study of this character was a cooperative investigation (13) of the experience of 34 life insurance companies of persons insured between 1869 and 1899

TABLE 1

Ratio of actual to expected deaths among men of average weight with one parent dead under 70 from specified condition*

By age at issue, first five policy years excluded
Experience of 34 life insurance companies, 1869-1900 (Specialized Mortality Investigation)

AGE GROUP WHEN INSURED (YEARS)	PER CENT ACTUAL OF EXPECTED DEATHS				ACTUAL DEATHS			
	Parent dead under 70 from:				Parent dead under 70 from:			
	All groups combined	Heart disease	Kidney or Bright's disease	Apoplexy or paralysis	All groups combined	Heart disease	Kidney or Bright's disease	Apoplexy or paralysis
All ages (15-70)	93.7	89.1	88.2	97.7	6,409	1,922	826	3,661
15-28	71.6	66.8	75.5	73.8	777	257	152	368
29-42	89.4	87.8	83.2	92.0	3,030	964	404	1,662
43-56	111.0	104.3	115.5	113.4	2,227	612	249	1,366
57-70	104.3	103.2	62.5	110.6	375	89	21	265

* Based on Farr's Healthy English Table, modified at ages 15-21 and 52-61.

and carried to the anniversary of the issue of the policy in 1900. The groups of interest to us in this investigation consisted of those persons of average weight, one or both of whose parents died under age 70 from heart disease, apoplexy or paralysis, and kidney or Bright's disease. The mortality in these classes by age groups at issue of insurance is shown in Table 1. We have left the earlier insurance years out of consideration because the standard mortality table used was a population table, and the adjustment to allow for the effect of medical selection in these earlier years was rather arbitrary. It will be noted that the mortality ratios are approximately the same in each of the groups; at all ages combined, all of them have a mortality below the expected. The results appear especially favorable at the younger ages at entry. The only marked deviations occur at the most

advanced ages and the comparatively favorable result among the older risks with a family history of Bright's disease is based on a relatively small number of deaths. In great part these differences in the mortality ratios at the various ages reflect a fundamental defect in the mortality standard because the table used did not represent a contemporaneous mortality experience but one which was considered by the men conducting the study to be the most suitable for the purpose. Actually the rates in the table were too high at the younger ages and too low at the older ages. The value of the study is also impaired by the high limit of age of the parent at death.

No facts are available with respect to the cause of death of the insured.

The Medico-Actuarial Mortality Investigation (1885-1909). The second important source of information is the cooperative investigation based upon the records of 43 life insurance companies, known as the Medico-Actuarial Mortality Investigation (14). This covered selected groups of persons insured between 1885 and 1908 who were traced to the anniversary of the policy in 1909. This investigation included two classes that are of interest to us, namely, those with two or more cases of heart disease and two or more cases of apoplexy or paralysis in the family record (parents, brothers and sisters). In the study of these cases, however, no limit was put upon the age at death of the parent or sibling. The results in these two classes separately and combined are shown in Table 2. The mortality in these two groups for all ages combined was approximately the same; both were moderately in excess of the expected. In this study, however, the results were much more favorable at the older ages of issue than at the younger ages.

Only brief consideration was given to the cause of death of the insured and the only information given in the report was to the effect that the mortality from heart disease was above normal in the group with a family record of heart disease, and that from cerebral hemorrhage and apoplexy was twice the normal in the group with a family record of apoplexy.

Experience of the Mutual Life Insurance Company (1885-1909). Dr. Brandreth Symonds (15), Medical Director of the Mutual Life Insurance Company made a special analysis of that portion of the experience contributed by his company, to the Medico-Actuarial Investigation on insured persons with two or more cases of apoplexy in the family record. He distinguished those with (a) an indeterminate family record of longevity (one or both parents living and under 70); (b) those where both parents reached 70; (c) those where both parents died under 60, and (d) an intermediate family record. As against the mortality of the entire experience, 124 per cent actual of expected deaths (85 actual deaths)—among men with two or more cases of apoplexy in the family record, those with a good history of parental longevity had a mortality of only 102 per cent, (27 deaths) those with an intermediate record, 157 per cent, (24 deaths) those with a poor record, 301 per cent, (8 deaths) and those with an inde-

terminate history, 109 per cent (26 deaths). While the experiences were small, they show definitely a relatively high mortality among men with a record of two or more cases of apoplexy in the family record, except where both parents died at relatively advanced ages. The experiences were too

TABLE 2

Ratio of actual to expected deaths among men with two or more cases of specified conditions in their family record†*

By age groups at issue. Experience of 43 life insurance companies, 1885-1909 (Medico-Actuarial Mortality Investigation)

AGE GROUP WHEN INSURED (YEARS)	PER CENT ACTUAL OF EXPECTED DEATHS			ACTUAL DEATHS		
	Both groups combined	2 or more cases in family record of:		Both groups combined	2 or more cases in family record of:	
		Heart disease	Apoplexy or paralysis		Heart disease	Apoplexy or paralysis
All policy years						
All ages (15 and over)	110	113	108	607	233	374
15-29	140	119	164	43	19	24
30-39	121	126	116	124	57	67
40-49	111	113	109	194	72	122
50 and over	100	104	98	246	85	161
Sixth & later policy years						
All ages (15 and over)	118	118	118	362	133	229
15-29	153	144	161	21	10	11
30-39	129	119	137	71	28	43
40-49	113	120	109	113	41	72
50 and over	114	113	115	157	54	103

* Based on Medico-Actuarial Mortality Table (contemporaneous mortality experience of the 43 companies).

† Parents, brothers or sisters.

small, however, to permit one to attach much significance to the variations according to the age of the applicants when insured. No details were given as to the causes of death of the insured.

Medical Impairment Study. Interest in the subject was dormant in life insurance medical circles, so far as active investigation is an index of such interest, for many years. In the next large-scale inter-company investi-

gation, the Medical Impairment Study of 1929 (16), the only class studied because of a poor family record of vascular disease consisted of those with two or more cases of apoplexy in the family under age 60, (parents, brothers, or sisters). One company submitted its experience on such applicants without regard to the age of the parent or sibling affected. This study covered the combined experience of 39 companies on applicants insured between 1909 and 1926 and traced to the policy anniversary in 1927. The results are shown in Table 3.

The inter-company experience on the cases with poor parental longevity gave an average mortality—101 per cent of the expected. There was no significant variation in the results according to the age of the applicant

TABLE 3

Ratio of actual to expected deaths among insured persons with two or more cases of cerebral hemorrhage, apoplexy or paralysis in family record (parents or siblings) when insured*

By age groups at issue. Cases insured in 1909 to 1927, traced to policy anniversary in 1928 (Medical Impairment Study, 1929)

AGE GROUP WHEN INSURED (YEARS)	COMBINED EXPERIENCE OF 38 COMPANIES, TWO OR MORE CASES UNDER AGE 60		EXPERIENCE OF ONE COMPANY, TWO OR MORE CASES AT ANY AGE	
	Per cent actual of expected deaths	Actual deaths	Per cent actual of expected deaths	Actual deaths
All ages (15 and over)	101	82	107	215
15-39	117	22	165	36
40-49	97	31	125	81
50 and over	96	29	86	98

* Based on Basic Table of Mortality, 1909-1927 (contemporaneous mortality experience of 10 large life insurance companies).

when insured. The mortality from cerebral hemorrhage accounted for 9 of the 82 deaths, or approximately twice the expected number. No facts are available with regard to deaths from other diseases in the cardiovascular-renal group.

The mortality among the cases submitted by one company without limitation as to the age of the affected relatives was somewhat above average—107 per cent of the expected. The ratios were definitely higher at the younger ages of issue, namely, 166 per cent among applicants 30 to 39 years old at issue, and 125 per cent among those 40 to 49 years old. The applicants over 50 had a mortality somewhat better than average. Of the 215 deaths, 88 were accounted for by cerebral hemorrhage and apoplexy, organic disease of the heart and Bright's disease. In the aggregate, this was approximately 50 per cent above the expected. The greatest rela-

tive excess was for cerebral hemorrhage which accounted for 37 deaths, or over twice the expected.

Provident Mutual Life Insurance Company (1908-1928). Edward W. Marshall (17), in a study of parental history and longevity segregated a group with both parents dead, one or both of them from a degenerative disease or "allied" cause. This list of causes was by no means a pure group, but a family record of cardiovascular disease accounts for most of the cases. Among those both of whose parents died from any of these causes, the mortality was 120 per cent of the expected, but the ratio reached 163 per cent in the small experience on those both of whose parents succumbed to any of these diseases before age 60. Among those with only one parent dead from any disease in this group, the mortality in three separate categories was ascertained. These groups and their ratios were: 1) Both parents dead and under age 60, 108 per cent; 2) one parent dead under age 60 and one over age 60, 109 per cent; and 3) both parents dead over age 60, 89 per cent. No details were published regarding the experience by age groups at issue, nor regarding causes of death.

Metropolitan Life Insurance Company (1899-1939). In the course of a new and long-term investigation of inheritance of longevity from life insurance records of our company, we segregated cases in which the insured reported two or more deaths under age 60 from any cardiovascular-renal disease in his family (parents or siblings). We had a record of approximately 325 such males, between ages 20 and 64 years, insured during the period 1899 to 1905. These have been traced to the policy anniversary in 1939, and their mortality has been measured against the contemporaneous experience on all men insured. There were only 11 cases with three members deceased before age 60 from cardiovascular-renal diseases and none with more than three. These cases are rare because they would usually be rejected for standard insurance. In slightly less than half of the total cases, both parents had died from one of these conditions. Most of the remaining cases were equally divided, with respect to the family record of cardiovascular-renal disease, among (a) father and one sibling; (b) mother and one sibling; and (c) two siblings.

The total number of years of life observed on the cases in this study slightly exceeds 4,000, or an average of 13 years on each individual. The results are summarized in Table 4. Of our group, 89 have died. These deaths are nearly 40 per cent in excess of the number expected. The mortality has been relatively worse during the first half of this long period of observation than in the later years. The experience in the first five years after issue may be disregarded because of the strong effect of medical selection in this period. In the sixth to twentieth years combined after issue of insurance, the mortality ratio is nearly 60 per cent above the expected, as compared with only a 15 per cent excess in the twenty-first to fortieth years.

The mortality ratios of these persons with a record of two or more deaths in the immediate family from cardiovascular-renal diseases show a progressive increase with age. In the small experience on those between ages 20 to 29 at issue, the mortality is slightly but not significantly below the standard, and among those between 30 and 39 at issue only moderately above normal. The ratios rapidly increase among risks past 40, with a ratio of 147 per cent for those between ages 40 and 49 at issue and 185 per cent for those 50 to 64 at issue. The number of deaths in these detailed age groups is too small to give reliable ratios when further classified by duration, but when the broad groups under age 40 and ages 40 and over at issue are considered, we find that among the younger risks at issue, the mortality ratio is slightly but not significantly higher during the sixth to

TABLE 4

Ratio of actual to expected deaths among insured men with two or more deaths under age 60 from cardiovascular-renal disease in family record (parents or siblings) when insured*

By age groups at issue. Cases insured, 1899-1905, traced to policy anniversary in 1939. Metropolitan Life Insurance Company, Ordinary Department.

AGE GROUP WHEN INSURED (YEARS)	PER CENT ACTUAL OF EXPECTED DEATHS			ACTUAL DEATHS		
	Duration of insurance			Duration of insurance		
	Total 1-40 years	6-20 years	21-40 years	Total 1-40 years	6-20 years	21-40 years
All ages (20-64)	137	159	115	89	47	30
20-29	92	120	108	5	3	2
30-39	113			28	12	13
40-49	147			31	16	10
50-64	185	189	124	25	16	5

* Based on contemporaneous mortality experience among all male lives.

twentieth years after issue than in the subsequent years, but among those over 40, the mortality is very appreciably higher in the earlier period, the ratio being nearly twice the expected during the sixth to twentieth years, but only one and one-quarter times the expected in the later years.

As Table 5 shows, deaths from cardiovascular-renal diseases accounted for 46 of the 89 deaths as against only 26 expected. The actual deaths from these causes exceeded the expected number by 75 per cent. The mortality from them is well above average in every subdivision by duration and by age. As was the case for all causes combined, the ratios were appreciably higher during the sixth to twentieth years after issue of insurance than in the later years. In the former case, the actual deaths from these diseases were over twice the expected, as compared with one and one-half times in the later insurance years. In comparison with the

average mortality from these causes for their age, the situation is worse among the older men than among the younger. Among those between ages 20 and 39 at issue, the mortality from the cardiovascular-renal diseases was one and one-quarter times the normal, as compared with a ratio of over twice the normal among those between ages 40 and 64 at issue. Among the younger risks, there was no significant difference in these ratios when further classified by duration of insurance, but among the older risks, the mortality during the sixth to twentieth years was about two and one-half times the expected, as compared with one and a half times in the subsequent years.

The excess mortality among these men with a poor family record of cardiovascular-renal diseases, therefore, was almost entirely accounted for by the very high death rate from these conditions. The mortality

TABLE 5

Ratio of actual to expected deaths from cardiovascular-renal diseases among insured men with two or more deaths under age 60 from cardiovascular-renal disease in family record (parents or siblings) when insured*

By age groups at issue. Cases insured, 1899-1905, traced to policy anniversary in 1939. Metropolitan Life Insurance Company, Ordinary Department.

AGE GROUP WHEN INSURED (YEARS)	PER CENT ACTUAL OF EXPECTED DEATHS			ACTUAL DEATHS		
	Duration of insurance			Duration of insurance		
	All years 1-40	6-20 years	21-40 years	All years 1-40	6-20 years	21-40 years
All ages (20-64)	177	220	143	46	22	20
20-39	126	129†	134	13	4	9
40-64	210	260	151	33	18	11

* Based on contemporaneous mortality experience among all male lives.

† Ratio not reliable because of small number of deaths.

from all other causes of death in the group was approximately normal, and for no other single cause was the number of deaths sufficiently large to show a statistically significant departure from normal. It is notable that among the older risks, 60 per cent of the total deaths are accounted for by the cardiovascular-renal group, and in the longer durations in this older group, 11 of the 15 deaths were from cardiovascular or renal disease.

SUMMARY AND CONCLUSIONS

These several studies point to a definite relationship between parents and offspring with respect to cardiovascular diseases. The clinical studies have generally shown that among patients with any form or symptom of the diseases, there is a high incidence of these diseases or symptoms in the parental history. In the insurance studies, it has been found that the total

mortality of persons with a family history of these conditions has ranged from approximately normal to well above normal, but in every study in which the death rate from chronic cardiovascular or renal diseases was considered, the mortality from them has been above average. In none of the studies was the mortality of these cases low, even though on the basis of the survivorship of the parents to advanced ages, the history was favorable. It is fair to conclude, therefore, that these studies indicate a familial relationship in the cardiovascular diseases.

The nature of this association cannot be brought out with any great exactness from insurance studies, or indeed from most of the material thus far collected on the subject. It is not likely that this association is a matter of direct inheritance of faulty cardiac or vascular structure in most instances, but rather that a number of factors are involved. For example, insurance studies have shown that the mortality from the cardiovascular-renal diseases is appreciably higher among the obese than among persons of slighter build. Since there are strong hereditary factors in body build or structure, the effect of heredity as regards the incidence of cardiovascular disease may be an indirect one.

The mortality from cardiovascular diseases among those with a family record of early deaths from such diseases is, however, not free from the influence of non-hereditary factors which tend to raise the mortality from them. For example, individuals orphaned at a relatively early age, regardless of the cause of death of the parents, are subject to deleterious environmental conditions associated with broken homes. Among children in such families, the frequency of infections leading to early cardiovascular or renal disease is relatively high. Moreover, many of these children must work at an early age and, consequently, often at unskilled or semi-skilled occupations, and among persons in such occupations the mortality from cardiovascular-renal diseases is appreciably above average.

The question may properly be raised whether a familial association with any cardiovascular disease or its symptoms is unfavorable to longevity. For, if such relationship involved no diminution in longevity, this relationship, while of medical interest, would be of no great consequence. This is by no means the case. The presence of these diseases in abnormal frequency in the family history at an early age is often an indication of the existence of those factors which produce early vascular degeneration. This is indicated by the fact that the excess death rate from these diseases among the persons we have studied is not concentrated at the older ages, and at the longer durations of insurance, but is present at every age and apparently is relatively worse for the shorter durations than the longer ones. Consequently, a great proportion of the deaths of these persons with a poor family record of cardiovascular disease occurs at relatively young ages. A family record of this type must, therefore, be considered generally unfavorable to longevity.

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THE NEPHROTIC CRISIS

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A typical complication of the nephrotic syndrome is the occurrence of acute febrile episodes with symptoms of peritonitis. The attack may take place without warning and with dramatic suddenness, ushered in by an abrupt rise in temperature to as high as 106°F. in 3 or 4 hours, often accompanied by a chill, and always by generalized abdominal pain and rigidity, nausea, vomiting and prostration. To this typical picture Farr (10) has given the name "nephrotic crisis."

There is a marked leucocytosis ranging from 20,000 to 40,000. In many instances, but not in all, blood cultures, especially if taken early, and cultures of peritoneal fluid will demonstrate the presence of a pathogenic organism; it is most commonly a pneumococcus, but not infrequently other organisms are found. The hemolytic streptococcus, bacillus coli, hemophilus influenzae and bacillus Morgagni have all been obtained in cases in this hospital. In some instances the acute illness lasts 36 to 48 hours, and is followed by a recovery almost as abrupt as the onset. In others there is a persistence of high fever and bacteremia with death occurring in the course of 10 days to 2 weeks. Such generalized infections have been seen in nephrotic patients ranging in age from 2 to 26 years and appear to be as common among males as females. Recurrences in the same patient are frequent and may or may not be accompanied by infection with the same organism.

Some patients show all the above signs and symptoms of peritonitis without demonstrable organisms in the blood or peritoneum. Such patients as a rule recover in 12 to 24 hours.

In this paper all such acute febrile episodes of the type described, whether or not infection was demonstrated, will be termed nephrotic crises.

A systematic study of the metabolic changes accompanying these acute episodes was carried out in this hospital by Farr (1) and by Farr and MacFadyen (2). These investigators observed that an accelerated loss of urinary non-protein nitrogen, resulting frequently in a negative nitrogen balance, regularly preceded by several days the onset of the crisis. They also noted that with onset of the crisis there was a further drop in the already low plasma albumin concentration to the neighborhood of 1 per cent or lower, and that a rise to the previous level accompanied recovery.

These findings indicated a disturbance in nitrogen metabolism before and during the nephrotic crisis, and led Farr and MacFadyen to an investigation of the non-protein nitrogenous constituents of the blood of nephrotic patients. Among the substances investigated the only significant changes found were in the plasma amino acids.

For the plasma amino acid analyses advantage was taken of the recently developed ninhydrin-carbon dioxide method of Van Slyke and Dillon (4) for the quantitative estimation of free alpha-amino acids. This method determines no amines other than the amino acids, and is therefore more specific than the nitrous acid procedure (3). MacFadyen and Van Slyke (5) devised an application of the ninhydrin-carbon-dioxide method to plasma which was sufficiently rapid and simple to serve as a routine clinical test. The normal level of alpha-amino acid nitrogen in human plasma was found to range from 3.5 to 5.0 mg. per 100 cc. These normal figures have been confirmed by Dr. Goettsch (6) at the Babies Hospital in New York City, using the same method.

By means of this technique, Farr and MacFadyen (2) found that in patients with the nephrotic syndrome, during periods without crises, the plasma amino acid nitrogen level was consistently below normal, ranging from 2.5 to 3.5 mg. per 100 cc. They also found that during the acute nephrotic crisis, with or without demonstrable infection, there occurred a further drop to a figure usually below 2.5 mg. per 100 cc. The figure 2.5 they arbitrarily termed the "critical level." Recovery was found to be associated with an abrupt rise in plasma amino acids in the direction of normal. These changes in plasma amino acids constituted the most characteristic metabolic abnormality noted in the nephrotic crisis, whether or not infection was demonstrated. With few exceptions, in cases in which plasma amino acid values significantly below the critical level have been observed, typical crises either have been present or have occurred within the next 2 or 3 days. Conversely, in observations of 44 crises, none has been seen in which the plasma amino acid level failed to drop, or which did not terminate with recovery when the amino acid level rose above the critical value. The accompanying charts illustrate these points graphically.

Figure 1 shows the febrile response to a series of five consecutive crises, accompanied by transient bacteriemia, in a 3 year old nephrotic girl observed by one of the writers (E) over the course of 3 months. Each episode was a typical nephrotic crisis, and during the periods of temperature elevation all the signs and symptoms of peritonitis were present, whereas during the periods of normal temperature the child appeared perfectly well. The remarkably close correlation between the elevation of temperature and depression of amino acids below the critical level is apparent.

Figure 2 illustrates the same phenomenon in another patient, a 4 year old boy, with a somewhat more prolonged period of infection.

Figure 3 illustrates a nephrotic crisis which is unusual in several respects. The patient was in an older age group. Her symptoms began as

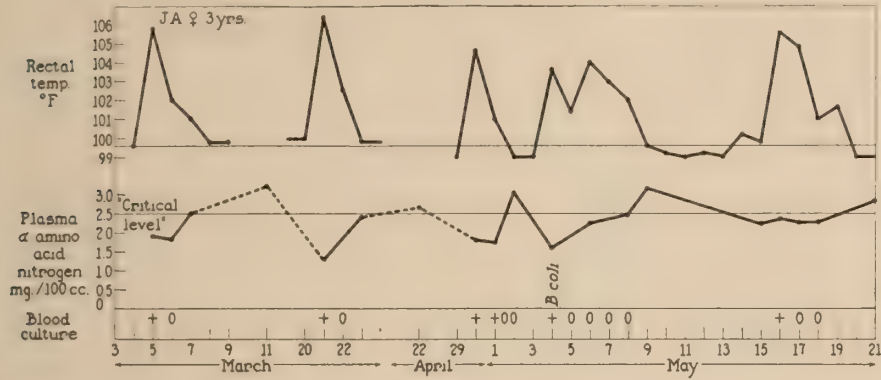


FIG. 1

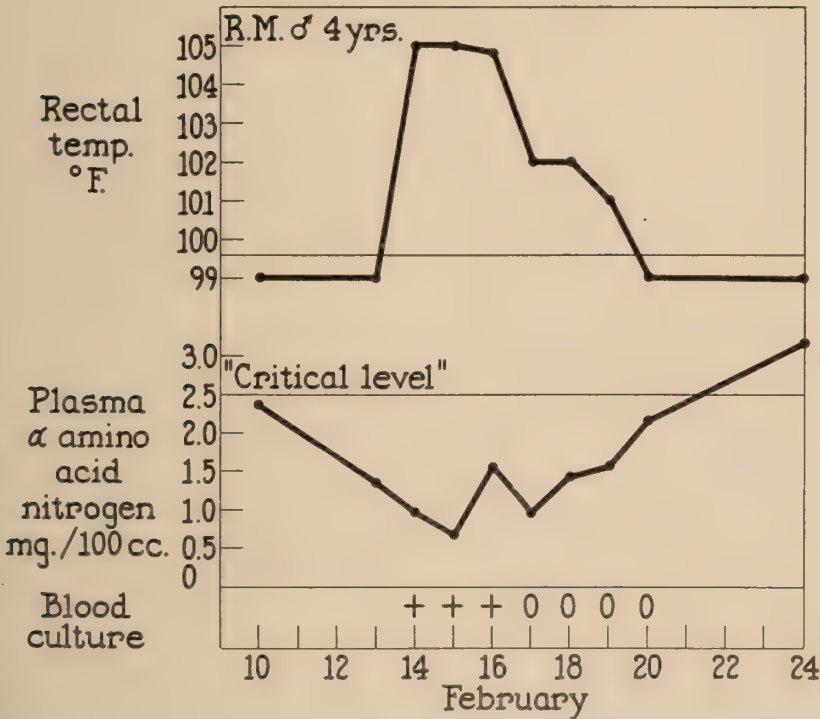


FIG. 2

a pelvic peritonitis associated with menstruation and remained localized for 2 days. During this time the plasma amino acid level, although showing a downward trend, continued slightly above the critical level. Sub-

sequently there was a further fall and the level remained depressed until death occurred on the ninth day of the crisis. This crisis is the only one which has terminated fatally in this hospital since the plasma amino acid changes have been under observation, accompanied by amino acid therapy.

The so-called critical level of 2.5 mg. of amino acid nitrogen per 100 cc. of plasma is a figure established by observations on children exclusively

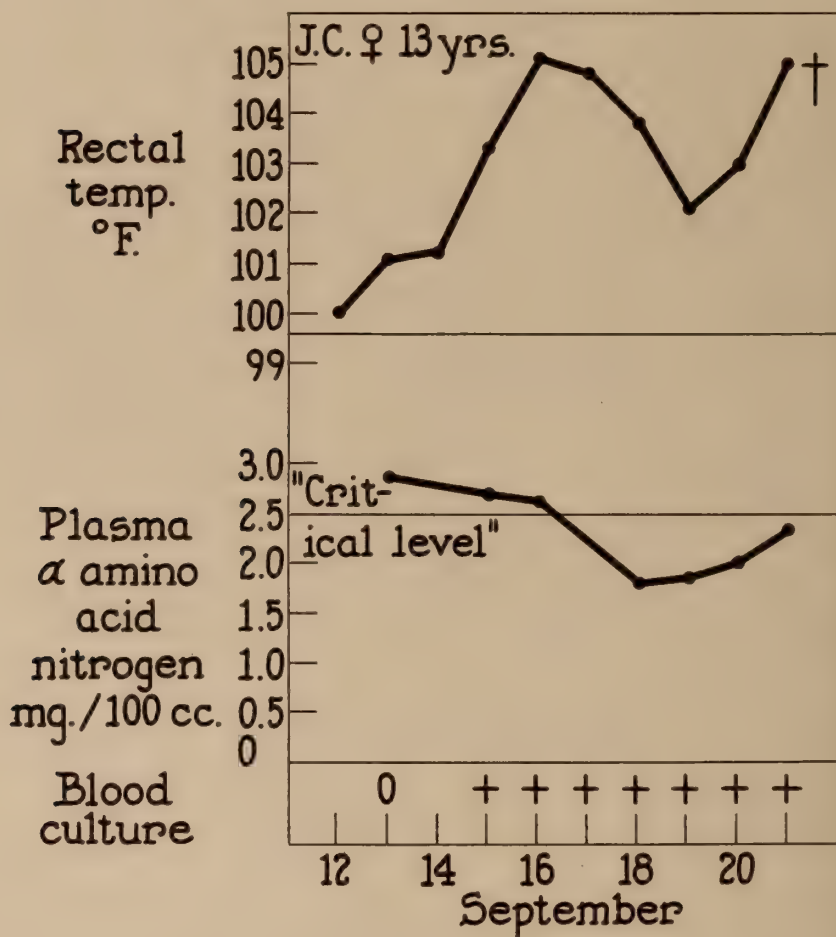


FIG. 3

under 10 years of age. The critical level may not be found at 2.5 mg. in all children when a larger number has been observed, and it may be different in adults. For this reason it may be more important, at least as far as prognosis in a given crisis is concerned, to emphasize the trend of the plasma amino acid curve rather than the absolute level at any one moment.

The demonstration of a plasma amino acid deficiency in the nephrotic syndrome has led logically to attempts to replace the missing amino acids. Gastrointestinal symptoms are so acute that feeding is impracticable; consequently the amino acids have been given intravenously. Elman (7) in St. Louis was the first to show the clinical practicability of administering amino acids intravenously in the form of a casein hydrolysate. Farr, Emerson, and Futeher (8) utilized this material,¹ both in attempts to raise the plasma amino acid level by prolonged treatment in patients not in crisis, and in the treatment of the acute nephrotic crisis. In patients not in crisis no effect occurred on the level of plasma amino acids or proteins or on the apparent clinical course of the disease. Nevertheless, it was shown that the nitrogen supplied by this method was utilized as efficiently and completely as dietary nitrogen (8, 9), so that it presumably served to combat the malnutrition that is so typical of nephrosis. In the treatment of the nephrotic crisis, when adequate food ingestion is usually impossible, nitrogen catabolism is accelerated, and malnutrition tends to be exacerbated, the use of intravenous amino acids seems logical if for no other reason than to maintain nutrition. It cannot be claimed that this form of treatment has either prevented the occurrence or shortened the course of the nephrotic crisis. However, the fact remains that prior to the introduction of amino acid therapy the mortality from crises with acute infection was 66 per cent in this hospital (10), whereas in 32 crises among 11 patients under 10 years of age treated with amino acids and with no other change in therapy there have been no deaths. The older patient depicted in figure 3 has been the only fatality among cases treated with amino acids. Besides belonging in an older age group, she had an infection which was resistant to sulfapyridine.

DISCUSSION

MacLeod and Farr (11) observed that nephrotic children carry for long preliminary periods in their throats the same organisms that ultimately invade their blood streams during nephrotic crises. When a crisis is accompanied by bacteriemia, the latter appears to result not from a fresh, virulent infection, but rather from a sudden decrease in resistance to an organism towards which the patient had previously acted as a carrier. Hence it appears possible that the bacterial invasion may result from a breakdown of immunity caused either by the hypoaminoacidemia or by the unknown metabolic disturbance which may cause both the forerunning negative nitrogen balance and the hypoaminoacidemia.

In some instances (e.g., fig. 2) where measurements were made from 1 to 3 days prior to the onset of a crisis, the plasma amino acids had already begun to fall. This would indicate that this drop is a reflection of

¹ The casein hydrolysate, used in these studies, was kindly supplied by Mead Johnson & Co., Evansville, Ill.

an underlying metabolic disturbance which precedes the clinical symptoms of the nephrotic crisis.

In the course of the ordinary upper respiratory or other infections in nephrotic children no changes in the plasma amino acid level have been noted (2). However, preliminary studies have given some indication that amino acid metabolism may be affected in conditions other than nephrosis, for it has been found (12) that during the acute phase of pneumonia the plasma amino acid level is depressed, and that with recovery there is a return to normal levels.

In 19 out of 44 nephrotic crises observed in 14 patients no infection could be demonstrated by repeated blood cultures. In such cases, one cannot exclude the possibility of a transient bacteriemia which may have disappeared before the first blood culture was taken; the observed bacteriemia is sometimes so transient that, after a positive culture at onset, a second culture 6 hours later may be negative. However, in view of 43 per cent of crises with negative cultures, the possibility cannot be ignored that the whole clinical picture in cases without demonstrable bacteriemia may be capable of production by a purely metabolic disturbance, without bacterial invasion as either a primary or secondary factor.

SUMMARY

The acute febrile attack with severe gastro-intestinal symptoms is described which occurs and recurs typically in nephrotic children, with or without demonstrable bacteriemia. Work by Farr, MacFadyen, MacLeod and their collaborators is cited showing that the attack is preceded by a metabolic disturbance evidenced by a loss of body nitrogen and by a dramatic fall in the plasma amino acid content. Recovery is regularly accompanied by a rise in the plasma amino acid content. Intravenous nutrition with amino acids seemed beneficial in reducing the mortality.

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THE AURICULAR WAVE (P) OF THE HUMAN ELECTROCARDIOGRAM IN NORMAL AND PATHOLOGICAL STATES

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The P wave of the electrocardiogram, so named by Einthoven (1), represents the spread of excitation and of contraction from the sino-auricular node radially throughout the bodies of the auricles. The sino-auricular node lies at the upper end of the sulcus terminalis at the junction of the free border of the right auricular appendix with the superior vena cava, and may extend 2 cm. in length in man. The S-A node is as a hub of the wheel of auricular musculature, permitting the radial spread of physiological activity. There is no special conduction tissue in the auricle. Excitation and contraction, long separated, have again been joined by the work of Einthoven (1) who showed that the interval separating electrical and mechanical registration was shortened to the vanishing point by great increase in sensitivity of the myocardiograph. The spread of the electrical events of the auricle is well known and it has been amply shown that the first portion of the auricle to become electrically negative is the region of the S-A node. Wedd and Stroud (2), using the experiments of Lewis (3), plotted the arrival of the excitation wave on the contour of the P wave. In the auricle the earliest point at which activity is observed is the sino-auricular node. The P wave begins 0.01 seconds later, when there is activity in the mid-caval region or in the interauricular band. The time of the left appendix, the latest point to become active, falls on the summit or the plateau of P, intermediate points lying on the upstroke.

The normal human P wave is always upright in Leads I and II. In the third lead P may be upright, isoelectric or inverted. P is either rounded or pointed or may be slightly bifid. In the study of Shipley and Hallaran (4) P was of greatest amplitude in lead II in 90 per cent of a normal series. In the remaining 10 per cent the greatest amplitude was in either lead I or lead III. In this series the P wave varied from 0.5 mm. to 2.5 mm. in height. The average measurement for men was 1.41 mm. and that for women 1.30 mm. The limits of duration were 0.08 second to 0.12 second with an average of 0.09 second. There was no demonstrable correlation between the duration of the P wave and heart rate. No instance was encountered in which the P wave was notched and exceeded 2.5 mm. in height and 0.10 second in duration. The P wave was inverted in 5 per cent of the records and was seen only in lead III. A diphasic P wave appeared only once in lead II and thirty-one times in lead III. There is a

correlation between the incidence of inverted P waves and of diphasic or inverted T waves in lead III.

Auricular T wave (Ta). Between the end of P and the beginning of the QRS complex, the string shadow is near the isoelectric line but is rarely on the isoelectric level in all leads. This deviation is usually down and does not exceed 0.8 mm. (Shipley and Hallaran). This depression is called the auricular T wave and is especially well seen in the isolated auricular complexes of complete heart block. In some instances P is separated from the auricular T wave by a short isoelectric segment. The auricular T wave represents repolarization of auricular muscle and is opposite in sign to the P wave. Ta has a duration of approximately 0.16 second. Shipley and Hallaran found the maximum of Ta in lead II, in which it appeared in 90 per cent of their records. Ta occurred in lead I in 55 per cent and in lead III in 30 per cent of their records. It was encountered most frequently in leads I and II (50 per cent), in both leads II and III in 17 per cent and in all three leads in 11 per cent. The combination of Ta in leads I and III was never seen. The P-R level may occasionally be elevated.

Chest leads. The two leads in widest use are 4F and 4R. In the recent comparative study of the leads by Liebow and Cushing (5) they state that P in 4R is a positive deflection in 97 per cent of the 715 records, and a negative deflection in 0.69 per cent. It is isoelectric in 0.69 per cent and diphasic in 1.52 per cent. Slightly more than 95 per cent of the P waves were 1 mm. or more in height. The maximum deflection was 4 mm. In 4F P was positive in 37.2 per cent, isoelectric in 29.2 per cent, negative in 26.7 per cent and diphasic in 6.84 per cent. Of the positive deflections only 27.4 per cent were 1 mm. or more in height. Only 10.2 per cent of the P waves in this lead were both positive and at least 1 mm. in height. The maximum amplitude was 2 mm. In all of the cases P in 4F was similar to 4R in 1.39 per cent and P in 4R was exceeded in height by 4F in but 1.39 per cent. P in 4R was more often positive and more often larger than P in 4F. When chest leads are taken in the fourth interspace to the right or left of the sternum P may be inverted.

Factors influencing normal P wave. Influence of the position of the heart in the body, as determined by respiration or other factors, and of the periodic shift of the pacemaker within the node has been shown by Lewis, Meakins, and White (6). The influence of the extrinsic cardiac nerves on the P wave has been studied. Einthoven (7) showed that section of the vagus in dogs produced an elevation of P. This work was confirmed by Rothberger and Winterberg (8). The latter also showed that section of the accelerator nerves was followed by a decrease in the amplitude of P.

The P wave in the esophageal lead. In auricular esophageal electrocardiograms the outstanding feature of the P wave is its polyphasic form and the presence of an intrinsic deflection. Analysis of the P wave reveals that

in some cases a small wave precedes the P wave of lead II, attributed to activation of the sinoauricular node by Brown (9). The clinical use of esophageal leads is still of questionable value.

Influence of carotid sinus pressure. Carotid sinus pressure produces sinus slowing, decrease in the amplitude of P, auricular standstill, prolonged auriculo-ventricular conduction and auricular premature beats.

Wandering pacemaker characterized by a variation in the contour of P from upright to diphasic and isoelectric but without changes in the P-R interval is seen especially well in lead III in normal individuals. This is probable due to a shift of the pacemaker from the head to the tail of the sino-auricular node.

Vectorcardiogram. The movements of the spot which represents the P and T waves are very small and their details are lost in the black area surrounding the isoelectric point (Wilson and Johnston (10)).

P wave in children. P is slightly higher in children especially in lead I (Ashman and Hull (11)). P varies from 0.04 to 0.08 second, the average duration being 0.06 second. Notching of P₁ and P₂ occurs occasionally.

Exercise. The amplitude of P is usually increased after exercise, most often in lead III, then in lead II, lead IV and in lead I least often. With exercise the P-Q level is depressed to a maximum of 1 mm. (Pardee (12), Takenaka et al (13), and personal observations).

Emotion. F. Mainzer and M. Krause (14) have shown that P is often high and pointed just prior to operations. Bier (15) likewise found a high P wave during emotional states.

Neurocirculatory asthenia. F. Mainzer and M. Krause have described high and pointed P waves in this condition.

Notching of P wave is found as an isolated finding and is usually due to the disease of the auricular muscle, either in rheumatic carditis, in the acute or healed stage, hypertensive disease, coronary artery disease, and syphilitic heart disease. Toxic doses of digitalis and of quinidine may also cause this deformity of the P wave.

Mitral stenosis. The prominent P wave found in mitral stenosis is well known: it is widened, notched, bifid, or flat-topped. It is frequently greater than 2 mm. in height and is greater than 0.08 second in duration. Berliner and Master (16) showed the large P wave was due to hypertrophy of the right as well as the left auricle, whereas those cases with hypertrophy of the left auricle alone did not have abnormally high P waves. Great increase in the amplitude of P (3.5 mm. or more) was accompanied by tricuspid as well as mitral valve disease. The auricular T wave is prominent in mitral stenosis.

Hypertension. Wood and Selzer (17) described a P wave widened, of low amplitude, and frequently bifid or flat-topped. P usually measures 0.12 second in duration and rarely more than 1 mm. in voltage. This type of auricular wave occurred more frequently with increasing symptoms of heart failure and the authors suggested that the P wave changes were due

to left auricular stress. Hahn and Langendorf (18) also described abnormal depression of the P-R segment in left auricular strain in arterial hypertension. They explained this finding as the result of arteriosclerosis of the auricular arteries, causing insufficient blood supply.

Hyperthyroidism. P is increased in voltage, frequently over 3 mm. in height (Rose, Wood, and Margolies (19); Schmidt (20)) and P is reduced in amplitude after thyroidectomy (21).

Hypothyroidism, on the other hand, causes a reduction in the amplitude of P (22):

Coronary thrombosis. The P wave is increased in amplitude and occasionally P is notched and widened. In Master's series P was 2 mm. or more in some lead in 40 per cent of his cases of recent coronary thrombosis, due probably to distension of the left auricle (23).

Cor pulmonale. In right ventricular strain (and with it right auricular strain and dilatation), the $P_{2,3}$ wave increases in amplitude and is peaked. P has a voltage of greater than 2 mm. and frequently a duration of more than 0.11 second (Winternitz (24)). This abnormal type of P, called P-Pulmonale by Winternitz, is found in emphysema, kyphoscoliosis, chronic bronchiectasis and fibroid tuberculosis, especially with signs of cardiac insufficiency. Congenital heart disease with pulmonic stenosis is also responsible for this deformity of P. Nordenfelt (25) found 46 cases with a P-Pulmonale in 2000 electrocardiograms. Of these there were 21 with no evidence of heart or lung disease. He ascribed the large P wave to weakness of the vegetative nervous system and did not believe that it was a diagnostic sign of high pressure in the pulmonary artery.

Alkalosis and acidosis have no effect on the P wave. (Personal observations and curves of Barker et al. (26)).

Acute nephritis. Master reported P waves high, wide or notched, which he interpreted as evidence of failure of the left ventricle with dilatation of the auricles (27).

Auricular infarction. In both experimental and clinical auricular infarction changes have been noted in both the contour of the P wave and of the P-R interval (auricular T wave) (28, 29). The P wave may be changed in contour and the P-R interval may be depressed or shortened (a less frequent change). Because of the frequent normal depression of the P-R level, this sign is of doubtful value in the diagnosis of auricular infarction. Of greater value is the change in auricular mechanism, auriculo-ventricular nodal rhythm or auricular fibrillation.

Congenital heart disease. Large and notched P waves are seen frequently, especially in lead II. This finding may be due to auricular dilatation and hypertrophy (30).

Viscerocardiac reflexes. Reissinger (31) reported the disappearance of P waves during cholecystectomy when the traction was exerted over the liver. Experimentally, in dogs, nausea and vomiting produced no consistent change in the P wave (32).

Familial periodic paralysis. No change in the P wave was noted during attacks or after the administration of potassium (33).

Effect of Drugs. Atropine. Cheer et al. (34) studied the effect of atropine in a case of complete heart block (2 mg.) and found no change in the contour of P.

Digitalis. Digitalis slows the heart with regular sinus rhythm, but not to the degree seen in auricular fibrillation. In addition, sinus arrhythmia is frequently seen. The P wave is lowered in amplitude, especially in lead III where P may be inverted. Experimentally, Macleod (35) found that auricular systole was shortened by certain glucosides of the digitalis group.

Ergotamine. Merke and Eisner (36) and Lev and Hamburger (37) noted an increase in the amplitude of P following the use of Ergotamine in hyperthyroidism.

Epinephrine. Levine et al. (38) noted the following effects after injections of Epinephrine: 1) sinus arrhythmia, accentuated or mitigated; 2) premature auricular beats and 3) A-V nodal rhythm (39).

Calcium. Harris and Levin (40) noted the reduction in the amplitude of P and sinus bradycardia following the intravenous injection of calcium.

Potassium. Harris and Levin likewise noted a lowering of P following the intravenous injection of potassium.

Quinidine. Quinidine causes a change in the contour of the P wave increasing its duration and with it prolongation of auriculo-ventricular conduction. Auricular standstill may follow the termination of auricular fibrillation.

Pitressin. Starr et al. (41) showed in a clinical study that pitressin caused a diminution of the P wave from 2 mm. to 1 mm. in height.

Hypnotics. Takenaka (42) in studying dial, adalin, luminal, and sulfonal found no consistent change either in the P or in the auricular T wave.

Nicotine, and nitroglycerine cause no specific changes in the P wave.

Magnesium sulphate. Miller and Van Dellen (43) found that magnesium sulphate administered intravenously in dogs caused sinus tachycardia and increase in the voltage of P. Zwillinger (44), on the other hand, found no change in the P wave either experimentally in animals or in man after intravenous injection of 10 cc. of 25 per cent magnesium sulphate but observed a prolongation of the P-R interval during the stage of paralysis relieved by injection of potassium.

Insulin shock is frequently associated with increased amplitude of P_{2, 3}. Inversion of P in leads II, III and IV is also found (45).

Metrazol induced convulsions may produce auricular extrasystoles and slow auriculo-ventricular nodal rhythm.

Electrically induced convulsions cause little or no change in the P wave.

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THE USE OF SULFONAMIDES IN RENAL INSUFFICIENCY

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Soon after the introduction of the sulfonamides, it was painfully brought home to physicians that, despite their sovereign therapeutic virtues in many infections of the urinary tract, these drugs possess powerful nephrotoxic potentialities. Damage to the renal parenchyma and obstruction to the flow of urine by masses of crystals rank among the more redoubtable accidents of sulfonamide therapy even in individuals without antecedent renal disease. Renal complications have been yet more feared when these drugs are called for in a patient with previously diseased kidneys or in whom the infection has impaired renal function. In the latter circumstances there has also been fear of retention with resultant overdosage. Nevertheless, the danger from an infection may be so great that judicious evaluation of the comparative risks of the primary disease and the drug indicates sulfonamide treatment even in the presence of severely damaged kidneys.

The case reported here illustrates the successful, probably life-saving, action of sulfathiazole in lobar pneumonia in a girl with long-standing azotemia due to chronic pyelonephritis.

CASE REPORT

History (Adm. 467696). A schoolgirl, aged 13 years, was seen first August 4, 1938. Her illness had set in insidiously about 18 months before with weakness and pallor. These symptoms, which persisted, were attributed to nephritis because of the constant finding of protein and formed elements in the urine. There was no history of swelling.

The initial examination revealed no palpable edema. The blood pressure was 140 systolic and 102 diastolic. The heart was not enlarged. The kidneys were not palpable or tender. Ophthalmoscopic examination disclosed that the retinal arterioles were constricted and probably sclerotic. The urine was cloudy and contained "three-plus" protein. The sediment was dominated by numerous white blood cells, some of which were clumped. There were moderate numbers of hyaline and granular casts, more numerous renal epithelia, and between 3 and 10 red blood cells per high power field of the sediment of the centrifuged urine. The blood contained 58 per cent hemoglobin and 32 mg. per cent urea nitrogen. The concentration test revealed a maximum specific gravity of 1.017.

The clinical picture remained monotonously unchanged. The anemia persisted; liver and iron, as is characteristic of azotemic anemia, had no definite effect. There was always azotemia of moderate degree (urea nitrogen 22 to 40 mg. per cent). Concentrating ability remained impaired. Proteinuria was always present and the sediment invariably contained large numbers of white blood cells. The blood pressure

varied between 140 systolic and 100 diastolic and 150 systolic and 110 diastolic. There was never palpable edema. Because of the persistent pyuria it was felt that the diagnosis was almost surely chronic pyelonephritis rather than glomerulonephritis.

About a week before entering the hospital, the patient developed an upper respiratory infection. Two days before admission she became feverish and began to cough. The cough was but slightly productive of sputum, which was not bloody, and was followed by vomiting. The night before admission the temperature rose to 105°F. and she had a severe shaking chill. Vomiting was very severe. I saw her that night; physical examination elicited only slight dullness and perhaps somewhat feeble breath sounds at the left base.

She was admitted to the Semi-Private Pavilion of The Mount Sinai Hospital January 10, 1941. Physical examination revealed classical signs of consolidation of the left lower lobe: extreme dullness from the eighth rib down posteriorly and bron-

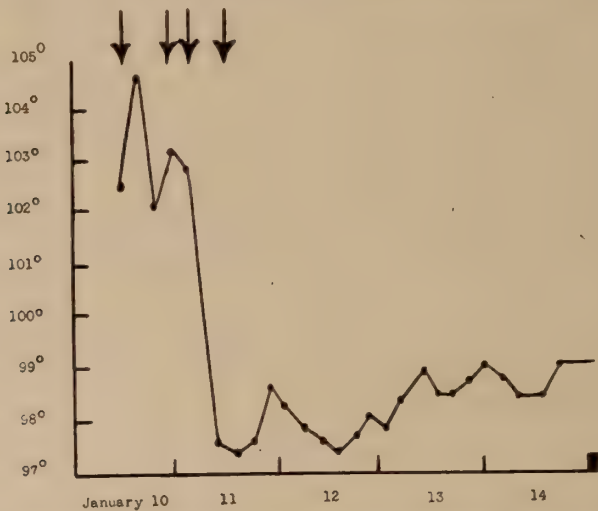


CHART 1. The temperature for the first five days is shown. Each arrow indicates the administration of 1 gram of sulfathiazole.

chial breath and voice sounds without râles. The blood examination showed: 67 per cent hemoglobin; 3,450,000 red cells; 62,000 white cells, of which 30 per cent were segmented polymorphonuclear leucocytes, 61 per cent non-segmented polymorphonuclear leucocytes, 8 per cent lymphocytes, and 1 per cent monocytes. The non-protein nitrogen of the blood was 100 mg. per cent. The sputum contained Type I pneumococci. Vomiting was severe. The respiratory rate on admission was 28 and the pulse rate 124 per minute.

The course of the temperature for the first five days is shown on the chart. Each arrow indicates the administration of 1 gram of sulfathiazole, although it is probable that some of the second dose was lost by vomiting. The fall in temperature was accompanied by subjective improvement, slowing of the pulse and respiratory rates to normal, fall of the strikingly high leucocytosis, and the usual physical signs of resolution.

January 14, the sulfathiazole content of the blood was 11 mg. per cent; January 20, the sulfathiazole in the blood was still 6 mg. per cent.

January 18, the temperature again started to rise and January 19 and 20 it reached

103°F. X-ray examination showed persistence of the consolidation in the left lower lobe but no evidences of fluid. Three 1 gram doses of sulfathiazole were given in the next 21 hours. The temperature returned to normal and this time remained down. The consolidation gradually cleared. The patient was discharged feeling as well as before the pneumonia and has remained in the same condition to the present.

The azotemia is shown by the following figures:

DATE	NPN (MG.%)	UREA N (MG.%)
1/10/41	100	
1/13/41		76
1/18/41		62
1/23/41		55
2/ 3/41		55
2/13/41		70
2/24/41		42

The urinary findings during the pneumonia were essentially unchanged from those described as present before. The pyuria persisted. Crystals of acetylated sulfathiazole were not seen on any of the many examinations. The urinary volume was low at first (vomiting), but when fluids were forced it rose to as much as 1860 cc. on January 15 and the same on January 16.

Summary. A girl with long-standing renal insufficiency and azotemia due to chronic pyelonephritis developed lobar pneumonia. The temperature fell to normal after the administration of less than 3 grams of sulfathiazole. A recrudescence of the pneumonia nine days later quickly receded after 3 grams more of sulfathiazole. Three days after 4 grams of sulfathiazole had been given the sulfathiazole content of the blood was 11 mg. per cent; 10 days after this dosage it was still 6 mg. per cent.

DISCUSSION

Renal insufficiency may conceivably modify three of the mechanisms by which the sulfonamides produce undesirable side-effects:

1) *Precipitation of the relatively insoluble acetylated sulfonamides* at any point in the urinary passages from Bowman's capsule to the urethra. Such precipitation may produce hematuria, renal colic, or obstructive oliguria or anuria. The precipitation is due to the presence in the urine of the acetylated sulfonamide in concentration higher than can be retained in solution. This occurs because the tubule is able to concentrate the acetyl sulfonamides far above the concentration in the plasma, even to more than a hundred times the blood level. Now, the common varieties of renal insufficiency, other than the uncomplicated impairment of filtration that occurs in acute glomerulonephritis and shock, are all characterized by diminished concentrating ability as a result of tubular damage. This diminished concentrating ability extends to all the urinary constituents and doubtless includes the sulfonamides. It, therefore, seems highly probable that renal insufficiency diminishes rather than increases the risk of precipitation of the sulfonamides in the urinary passages.

2) *Damage to the renal parenchyma by the sulfonamides.* On rare occasions the sulfonamides produce renal damage by some mechanism other than the precipitation of crystals in the urinary passages, i.e., they are directly nephrotoxic. Several instances have been observed in which renal function became impaired during the administration of a sulfonamide in the absence of hematuria, and in which discontinuance of the drug was followed by improvement of the kidneys. I have seen at least four such instances due to sulfathiazole in which uremia resulted and in which the outcome was fatal. In none was there any evidence that precipitation of crystals played a part. In one there was a necropsy, which revealed only uncharacteristic renal damage with regressive tubular lesions; there was evidence of neither obstruction by conglutinated crystals nor glomerulo-nephritis. It remains to be studied whether such direct chemical damage to the kidneys by sulfonamides is favored by previous impairment of renal function; the latter was not present in any of the cases that I observed.

3) *Effects due to action of the sulfonamides on organs other than the kidneys.* Sulfanilamide is excreted almost quantitatively (over 90 per cent most often) in the urine; sulfathiazole and sulfapyridine are also eliminated predominantly, though not as nearly exclusively, in the urine. One would, therefore, anticipate that impairment of renal function would result in a higher blood level of sulfonamide from a given dose, and that the drug would remain longer in the organism when kidney function is poor. These surmises have been borne out by actual experience; Long and Bliss (1) Bensley and Wilen (2), and others have found that in anuric patients or those with severely depressed renal function the sulfonamide level falls but slowly. Furthermore, it has been found that with a longer stay in the body due to poor renal function, a progressively higher fraction of the sulfonamide in the blood becomes conjugated to the inactive acetyl compound (Stewart, Rourke and Allen (3); Brown, Thornton and Wilson (4)).

These principles were exemplified in the case described above. The slow excretion of sulfathiazole in renal insufficiency resulted in the blood level of 11 mg. per cent 3 days after and 6 mg. per cent 10 days after the administration of only 4 grams of the drug. The dramatic therapeutic response with fall in temperature to normal after only 3 grams of sulfathiazole was doubtless favored by the larger amount of the drug in the organism due to negligible excretion in the urine. The recrudescence of the pneumonia after 9 days when the blood sulfathiazole level was still over 6 mg. per cent is plausibly accounted for by progressive acetylation and consequent inactivation of the sulfathiazole during its long stay in the body; unfortunately, no partition of the blood sulfathiazole into free and conjugated fractions was carried out. The absence of any effect on the pyuria while the pneumonia was so strikingly improved is in good accord with the low concentration of sulfathiazole in the urine and the high blood

level that result from renal insufficiency. Likewise, the absence of acetylated sulfathiazole crystals from the urine is doubtless also explained by the low concentration of the urine.

CONCLUSIONS

In the presence of renal insufficiency, persistently high blood levels and striking therapeutic effects may be obtained from very small doses of the sulfonamides.

However, relapse of the infection (pneumonia in the case here reported) may occur while the blood level of total sulfonamide is still high. This is probably largely due to progressive acetylation and consequent inactivation of the sulfonamide retained so long in the organism.

Because of the low concentration of the urine formed in chronic renal insufficiency, the high blood level is maintained despite far larger urinary volumes due to forcing of fluids than is the case with unimpaired kidneys.

The low concentration of the urine in renal insufficiency also renders massive precipitation of acetyl sulfonamide crystals less likely.

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THE ESTROGENIC REACTION IN ADRENAL CORTICAL CARCINOMA

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Seven years have elapsed since I first made the observation that in adrenocortical carcinoma an excess of estrogenic substances may be excreted in the urine (1). This observation was based on two cases. Three years later I again called attention to this readily elicited reaction (2) reporting two additional cases. At present six more cases can be recorded of which one gave a false negative test. During these seven years, an increase in our knowledge has taken place and many questions of interest have arisen, some of which will be taken up in this communication.

Cushing's concept of the so-called "basophilic syndrome" (3) focussed renewed attention upon a group of patients whom Bulloch and Sequeira (4) first described in 1905. Rolleston (5) gave a masterly description of the condition in 1925.

Investigation has shown that contrary to Cushing's concept, basophilic adenomata are a frequent finding and usually without clinical significance (6). Statistics demonstrate that the vast majority of the syndrome patients harbor an adrenal cortical carcinoma or adenoma (7). Occasionally cortical hyperplasia, probably overlooked in the earlier reports, causes the symptoms. Some evidence obtains that an increase of basophilic cells in the adenohypophysis may result secondarily from adrenocortical disease, and thus merely form part of the many bodily changes.

Clarification of our knowledge of the functions of the adrenal cortex throws much light upon the symptomatology. Several of the adrenal steroid hormones have been isolated in crystalline form (8) permitting an accurate pharmacological analysis of their actions (9) both on animals and upon human subjects. Likewise in standardizing their dosage, excess symptoms have been produced inadvertently, which in some instances temporarily have reproduced some of the manifestations observed in the adrenocortical syndrome (A.C.S.).

Desoxycorticosterone, in adequate dosage causes increase in the sodium and chlorides of the blood; diminution in potassium, urea and non-protein nitrogen. The effect on the calcium is less clearly understood. Apparently calcium is withdrawn from the bones with consequent decalcification, but Albright's explanation (10) that the decalcification may be due to lack of estrogens is not borne out by my observations. Desoxycorticosterone likewise elevates the blood pressure.

The cortical steroids are closely related in structure to the sex hormones and several manifest in addition to their cortical action, estrogenic progestational and androgenic qualities (11). Both in the normal and diseased individual, male and female sex hormones are elaborated in the two sexes, possibly as part of the excretory metabolism, but certainly in sufficient amount to play some rôle in the economy. If the production is excessive, clinical manifestations may appear.

The male factors (isolated from the urine in the form of androsterone, and dehydroisoandrosterone, in excess, cause hirsutes, acne, enlargement of the clitoris; the female factors in excess cause amenorrhea (as in pregnancy), perhaps plethora (12).

The chemical constitution of the secreted and excreted estrogens has not been clarified in the normal male and female, certainly not in the A.C.S., although Marrian (13) has isolated at least one abnormal steroid in this condition (pregnane 3-17-20 triol).

It might be anticipated that if androgen only were produced in excess that *masculinization* would develop, or that if the estrogens alone were predominant, *femininization* would result. Actually both factors have been found in larger amounts than normal in some of the carefully studied cases. Consequently the A.C.S. manifests itself in addition to the adrenal symptoms as a mixed picture of *bisexual over-function*.

The excess excretion of androgens first described by Callow (14), has been repeatedly confirmed (15). I first drew attention to excess estrogenic excretion in cortical carcinoma (1934 (1); 1937 (2)). This observation now, has been made on eight cases confirmed by operation or autopsy. In cortical adenoma and in cortical hyperplasia this excess was not demonstrable. While this excess has been confirmed by other observers (16) in some patients, it has been found absent in others. As the test is simple and easily applied, this seems to signify that variations may occur and that study of a larger material might be of value.

Furthermore, it would seem worthwhile to collect from the literature a large group of cases in which sex titres by reliable investigators have been obtained and in this collective group to analyze the symptoms. By this means, the part actually played by the male and female factors should become more apparent. It is readily understandable that the interplay of two variable factors might produce an infinite variety of systemic changes. The symptoms associated with the A.C.S. are moonface, abdominousness, high blood pressure, hirsutes, pink striae, plethora, decalcification, irrespective of sex, and in the female, amenorrhea or oligomenorrhea and enlarged clitoris; in the male, impotence.

The test is simple and is based on the demonstration of excess amounts of estrogen or of steroids with estrogenic properties, present in the fresh urine. I have found that neither acid nor bacterial hydrolysis materially affects the titre. Therefore, if the potent substances are normal estrogens,

this would signify that they are present in the uncombined form. As yet we are in no position to affirm this view because the chemical nature and physiological action of the substance or substances present is unknown.

The test was described fully in 1937 (2). "The performance of the test is extremely simple. A fresh specimen of urine is obtained. Of this a total of 1 and 2 cc. is injected subcutaneously in five divided doses spread over forty-eight hours into adult castrated mice (0.2 cc. x 5; 0.4 cc. x 5). After completion of the injections, the vaginal spreads are examined three times daily for three succeeding days. A positive estrogenic reaction manifests itself by the change of the vaginal spreads from leucocytes to cornified epithelial cells. In every case the urine must likewise be tested

TABLE I

Negative

	NO.	♀	♂
Hirsutes, obesity, high blood pressure, striae.....	27	23	4
Hirsutes and obesity.....	8	8	—
Hirsutes, severe.....	34	31	3
Obesity.....	10	9	1
Hirsutes and amenorrhea.....	17	17	—
Hypertension.....	8	8	—
Abdominal malignancy.....	9	6	3
Tumor of lung.....	5	—	5
Grawitz tumor kidney.....	4	—	4
Pubertas precox.....	3	1	2
Cortical adenoma adrenal.....	3	3	—
Pseudohermaphrodite.....	2	1	1
Varia.....	25	24	1
Adrenocortical carcinoma (uremia).....	1	1	—
	160	132	28

either by the Friedman or by the Aschheim-Zondek technic. The pregnancy test must be negative if any conclusions are to be drawn."

The pregnancy test must be performed both on *males* and females as a chorionepithelioma in the male could produce a high estrogenic reaction in the urine, and pregnancy in the female would have a similar effect.

Up to the present, 169 tests have been performed on a great variety of patients. Of these, 160 were negative, including one false negative, and 10 were positive with 2 false positives. There were in addition 2 weak positives (with 2.5 cc. of urine) both of which were false.

The negative reactions were obtained on a wide range of cases readily visualized in Table I.

Of the 160 negative tests, 36 were on individuals highly suspect in the eyes of numerous trained observers. They included 28 cases which embodied many of the symptoms ascribed to A.C.S. One case, to be dis-

cussed in detail, actually proved to be adrenocortical carcinoma (in terminal uremia). None of these cases, with the one exception, have as far as known, developed carcinoma of the adrenal. The 124 other cases serve as controls.

The single false negative was a woman who showed all the cardinal symptoms of A.C.S., including a lumbar tumor. Her age was forty-nine years (in the menopause); she was admitted in terminal uremia, the blood urea nitrogen rising from 40 to 100 mg. per 100 cc. Whether the menopause which usually is accompanied by marked diminution of estrogen, plays a role (although most investigators now ascribe the rise of sex hormones in the A.C.S. to adrenal cortical oversecretion) or whether defective excretion of estrogen, due to the uremia was causative (against which stands the fact that the androgenic excretion was excessive, 85 I.U. in 24 hours) must remain unanswered.

The 10 positive reactions are recorded in Table II. They include 8 patients with adrenal cortical carcinoma (operation or autopsy), one with malignant Grawitz tumors of both kidney and ovary, with lung metastases and one with generalized lymphosarcomatosis.

Weakly positive reactions, i.e. with 2.5 cc. of urine were obtained on two patients, one with genital macrosomia, male six years of age who has remained well for five years, and one congenital internal hydrocephalus.

In the adrenal carcinoma patients the amount of estrogenic potency per liter varied greatly in different patients and somewhat in different specimens from the same patient. In two patients an equivalent of 13,000 I.U. (estrone) per liter was found (one male with recurrence ten years after operation, one female). The lowest titre was 1000 I.U. per liter in two patients. The generalized lymphosarcomatosis showed only 500 I.U. per liter; the macrosomia as well as the hydrocephalus only 400 I.U. per liter.

In three patients with adrenal cortical carcinoma blood samples showed no excess of estrogen. The adrenal tumors contained comparatively little estrogenic material, averaging 1 I.U. per 5 g. of fresh tissue. The post mortem bile from one patient assayed one I.U. to 0.2 cc., or 5000 I.U. per liter which is high. In this patient the liver substance as well as the liver metastases contained one unit per 0.1 g.

Of interest is the fact that none of the many cases of hirsutes, 86, whether simple or accompanied by one or more of the syndrome hallmarks, gave a positive reaction. A negative reaction was noted in the three cases of proved (operation) adrenal adenomas.

Based upon these data it appears justified to concede considerable importance to the estrogenic reaction for diagnosis of adrenocortical carcinoma. A positive reaction (with 1 cc. or less of urine) if accompanied by a lumbar mass or visualization of an enlarged adrenal by perirenal insufflation, warrants a positive diagnosis of adrenocortical carcinoma.

Reactions produced by 2 cc. of urine (500 I.U. per liter) should be regarded as suspicious and warranting exploration of the adrenals if a lumbar mass and concomitant symptoms are present.

A repeatedly negative test in a patient with symptoms of A.C.S., with positive perirenal insufflation test, favors the diagnosis of adenoma or

TABLE 2

LAB. NO.	SEX	AGE	LESION	OP.	P.M.	URINE TITER	I.U.-ES. LITER	OTHER ORGANS	
2704	♀	36	A.C.C.	—	+	0.075	13,300	Bile 0.2	Hydr. urine 0.75
3005	♀	19	A.C.C.	—	+	0.2	5,000	Adr. t. 0.3 g., liver 0.1	Blood 40 cc. = 4
3256	♀	36	A.C.C.	+	—	1.0	1,000	—	Well
3876	♀	35	A.C.C.	+	+	0.1	10,000	Adr. t. 3 g., psoas 2.5 g.	Blood 10 cc. = 0
4583	♀	36	A.C.C.	—	+	0.4	2,500	—	Hydr. urine 1.5 cc. M.S.H. 103/
4615	♂	59	A.C.C.	+	—	0.075	13,300*	—	Male S.H. 77 I.U./24 hours
4716	♀	23	A.C.C.	+	—	1.0	1,000	—	Lung metast. urine again 1 cc. M.S.H. 119
4879	♀	28	A.C.C.	+	—	0.8	1,250	—	

False positives

4229	♀	42	Malign. Grawitz kid. & ov.	—	+	0.75	1,330	—	Pulm. met.
4628	♂	39	Gen. lymph-sarcomat.	+	+	2.0	500		
4218	♂	6	Hypergenitalism	—	—	2.5	400		M.S.H. 2.0/24
3470	♂	13	Cong. int. hydroceph.	—	—	2.5	400		

False negative

4834	♀	49	Adr. cort. ca. uremia	—	+		<250		M.S.H. 85/24 Urea? uremia
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adrenal hyperplasia. If both these tests (estrogenic and perirenal insufflation) prove negative, watchful waiting is advised.

Finally, it must be conceded that all the symptoms of the A.C.S. may result from pituitary or thymic neoplasms (see Oppenheimer and Silver (17)) and that a positive estrogenic reaction has been obtained in other conditions than adrenal cortical carcinoma. My interpretation of this is that symptoms and reaction are due to stimulation of the adrenal cortex by the underlying disease.

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COARCTATION OF THE AORTA—A NEW THEORY AS TO ITS PATHOGENESIS

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Coarctation of the aorta is a form of congenital heart disease of special interest because of increasing clinical recognition and the fact that many patients reach adult life. The mechanism underlying coarctation of the aorta is still obscure and in dispute. The numerous theories suggested either fail to accord with the facts or leave important observations unexplained. The purpose of this report is to offer a new theory, which is in greater harmony with the known data.

CLASSIFICATION OF COARCTATION OF THE AORTA

Coarctation of the aorta refers to a congenital constriction or atresia of the aortic arch in any of its portions, but usually in the descending part between the origin of the subclavian artery and the region of insertion of the ductus arteriosus. Since Bonnet's (1) classic paper in 1903, cases of coarctation of the aorta have been divided into the two major categories, *infantile* and *adult*. These arbitrary terms were employed because the former category usually represented the newborn or infants less than one year of age, while the latter occurred in children and adults. But the terms were inadequate because these two categories of cases were distinguishable by more important clinical-pathologic features and because the age distinction led to inclusion of one type of case with those of the other. Thus, subjects with characteristics of the so-called infantile coarctation not rarely lived into childhood and occasionally into adult life. Conversely, subjects with the adult type of coarctation may die in early infancy of some associated or intercurrent disease.

There are, however, two apparently different groups of cases of coarctation which correspond usually to the infantile and adult forms of Bonnet and which are distinguished by the following features:

	INFANTILE	ADULT
1. Site of coarctation.....	Above ductus	At or just below ductus
2. Ductus arteriosus.....	Open	Closed
3. Associated anomalies.....	Frequent, major	Major anomalies rare Minor anomalies frequent
4. Collateral circulation.....	Absent	Present

These and other differences lead to a sharp division of cases; if the terms infantile and adult are retained, classification of individual cases should be made on the basis of these features and not merely on the basis of the patient's age. Any theory as to the occurrence of coarctation of the aorta must account for this sharp division of cases and for each of the distinguishing features of the two groups. These features will be discussed in detail in connection with the theory to be proposed.

PREVIOUS THEORIES OF PATHOGENESIS OF COARCTATION OF THE AORTA

Two general theories may be distinguished, one of which interprets coarctation of the aorta as an early developmental or prenatal anomaly and the other as a postnatal defect related to closure of the ductus arteriosus. The prenatal developmental theory, first suggested by Reynaud (2) in 1828 and amplified by Rokitansky (3) in 1844, assumes that coarctation arises in the second month of life when the embryonic arches are undergoing involution and are being converted into the adult aorta, pulmonary artery and their branches. The coarctation represents, according to Loriga (4) and others, a defect in the development of the descending limb of the primitive left aorta, which joins the left fourth aortic arch with the left fifth and sixth arches. The chief evidence for this theory is the frequent association of numerous other anomalies such as: interauricular and interventricular septal defects, transposition of the vessels, and disturbances in the branches of the aortic arch. While these occur predominantly in Bonnet's infantile group, some of the same defects, particularly anomalies in branches of the aortic arch, occur in both the infantile and adult groups.

The postnatal ductus theory was proposed to explain two important observations. First, in the cases representing Bonnet's adult group, the coarctation of the aorta was a sharp, ligature-like localized constriction situated at the exact site of attachment of the ductus arteriosus which was almost always closed, or immediately below this site. Second, this particular form of coarctation was never seen in fetuses. Craigie (5), in 1841, first suggested that "the obliterating action, which had taken place in the ductus arteriosus, had been for some peculiar cause prolonged into the aorta, and had there given rise first to contraction and then to obliteration of the coats of that vessel." What this "peculiar cause" was or why closure of the ductus did not always produce coarctation of the aorta was not stated.

Skoda (6) suggested that a special form of tissue in the ductus led to its contraction at birth and that coarctation of the aorta resulted from extension of this peculiar tissue into the adjacent aorta (Skodaic theory). Brunner (7) adopted a similar explanation except that he postulated aberrant transplantation of this special tissue in various parts of the descending aortic arch, rather than direct extension. Subsequent studies have failed to reveal any special tissue concerned with the obliteration of the ductus

arteriosus (Klotz (8)). Constriction of the aorta near the ductus attachment has been attributed also to the mechanical effect of traction when the ductus is obliterated, but the possibility of such a mechanical effect has been rejected. Furthermore, such a theory fails to explain many associated findings.

Rokitansky (3), who favored the prenatal, developmental origin of coarctation of the aorta, assumed a primary weakness in the aortic wall of the isthmus (the region of the descending aortic arch between the origin of the left subclavian artery and the attachment of the ductus). Because of this weakness, he believed, the obliterating ductus arteriosus would cause the aorta to yield and become constricted, while the normal aorta would resist such a force.

Bonnet (1) adopted two different explanations corresponding to the two different forms of coarctation which he described. In the infantile group of cases, in which the constriction is usually a *diffuse* narrowing of the arch especially in the region of the isthmus above the insertion of the ductus, and in which there are frequent grave cardiac anomalies, he accepted a prenatal developmental abnormality as the basis of the lesion. In the adult form of coarctation, in which there was as a rule a sharp, localized constriction just at or immediately below the insertion of the ductus, and in which the ductus was almost always obliterated, he assumed that the constriction was a postnatal lesion associated in some uncertain manner with the closure of the ductus. Abbott (9) and, more recently, Evans (10) criticized this dual theory for what they believed was essentially an identical lesion in somewhat different areas of the aortic arch, especially since certain obviously prenatal abnormalities of the aortic arch were associated with the so-called adult form of constriction near the ductus as well as with the infantile type.

None of the theories thus far proposed have satisfactorily reconciled the observation of undoubtedly prenatal associated anomalies, indicative of a developmental origin for the adult as well as infantile cases, with the fact that the adult type of constriction is never seen in fetuses and is so obviously located in proximity to the attachment of a closed ductus arteriosus. If closure of the ductus is etiologically related to the occurrence of the adult type of constriction, no adequate explanation has been offered of the manner in which closure of the ductus produces aortic constriction.

A satisfactory theory for the occurrence of coarctation of the aorta will have to account for the different locations of the constriction in the two main clinical-pathologic groups of cases, for the sharp localization of the adult constriction to the region of insertion of the ductus, for the presence of grave cardiac anomalies in the infantile and their absence in the adult form, for the patency of the ductus in the former and its closure in the latter, and for the presence of so-called minor anomalies in the adult group of cases. In particular, these minor anomalies are those of branches of

the aortic arch, bicuspid aortic valve with frequent eventual rupture of the aorta indicative of weakness of the aortic wall, and the association of congenital subaortic stenosis. If closure of the ductus is related to the occurrence of aortic coarctation, a more satisfactory mechanism must be proposed than has been done hitherto. In the following pages I shall offer a theory which appears to satisfy these requirements in most if not all essential respects. First it will be necessary to review briefly certain

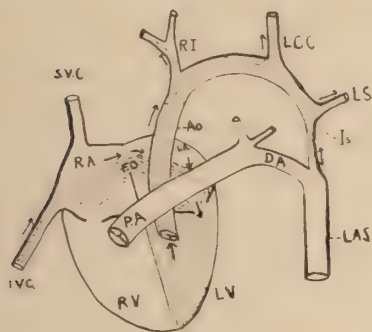


FIG. 1

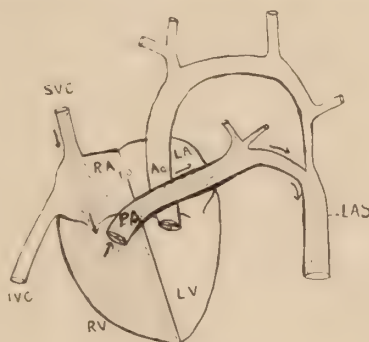


FIG. 2

FIG. 1. Fetal circulation. Upper aortic segment extending from left ventricle (LV) to insertion of ductus arteriosus (DA). Oxygenated blood from inferior vena cava (IVC) reaches left side of heart by way of open foramen ovale (FO) and supplies brachiocephalic vessels (RI, LCC and LS). Isthmus (IS), termination of upper aortic segment, is low pressure area extending from left subclavian (LS) to insertion of ductus arteriosus.

FIG. 2. Fetal circulation. Lower aortic segment (LAS) is descending aorta below insertion of ductus arteriosus. Unoxxygenated blood from superior vena cava (SVC) traverses right atrium (RA), right ventricle (RV), pulmonary artery (PA) and patent ductus arteriosus (DA) to lower aortic segment and lower half of body.

features of the fetal circulation and the mechanism of closure of the ductus arteriosus.

THE FETAL CIRCULATION IN THE AORTIC ARCH

It has long been believed that the oxygenated blood from the placenta and the blood from the lower half of the body, arriving in the right atrium by way of the inferior vena cava, and the unoxxygenated blood, arriving from the upper half of the body by way of the superior vena cava, are only partially mixed in the right atrium and continue as two distinct currents. That from the inferior vena cava is directed by its valve chiefly through the foramen ovale to the left atrium and thence through the left ventricle and ascending aorta and arch to the brachiocephalic vessels. Thus, this relatively more oxygenated stream from the inferior vena cava supplies the vital brain and heart as well as the upper extremities (fig. 1). At the same time, the unoxxygenated blood from the superior vena cava, after some mixing with oxygenated blood in the right atrium, is directed chiefly

through the tricuspid orifice to the right ventricle and trunk of the pulmonary artery. While toward the end of fetal life a small portion of this blood is sent to the lungs through the pulmonary vessels, most of the right ventricular output is directed through the patent ductus arteriosus into the descending arch of the aorta and thence to the lower half of the body (fig. 2).

Whether or not the concept of a fairly distinct separation of the superior and inferior vena caval blood in the right atrium is accepted, there is no doubt that the blood which arrives in the right atrium is divided into two streams, one of which goes by way of the foramen ovale to the left side of the heart and the ascending aorta, and the other to the right side of the heart and by way of the ductus to that part of the aorta which is distal to the attachment of the ductus arteriosus. That the latter pathway receives most of the blood and probably has the higher intravascular tension seems to be indicated by the fact that at birth the pulmonary artery and the right ventricle are considerably larger than the aorta and left ventricle.

The pressure head developed by the left ventricle is sufficient to send its blood into the aortic arch and its branches to the head and upper extremities. But it is likely that by the time the descending part of the arch (isthmus) is reached, distal to the origin of the left subclavian artery and proximal to the attachment of the ductus arteriosus, the pressure has fallen considerably and little if any of the left ventricular output mixes with the blood from the ductus arteriosus in the descending aorta (fig. 1). On the other hand, the right ventricular output passes through the main pulmonary artery and ductus, which is a tube of wide dimensions in fetal life, into the descending portion of the aorta beyond the region of attachment of the ductus without passing upward and mixing with the blood from the left ventricle (fig. 2).

In this way, despite their anatomic proximity, the aortic arch down to the region of the ductus arteriosus is part of the left ventricular circulation and practically completely segregated from the remainder of the aorta distal to the attachment of the ductus, which is part of the right ventricular circulation. Hereafter we shall refer to these two segments as the upper and lower aortic segments. One can conceive of these two segments as being as functionally distinct as the pulmonary and systemic circulations in the adult, the lower segment, which brings blood from the pulmonary artery and ductus for oxygenation to the placenta, corresponding to the pulmonary circuit, and the upper segment, which carries oxygenated blood from the left ventricle to the head and upper half of the body, representing the systemic circulation.

This division into upper and lower aortic segments is supported by the following observations: The terminal portion of the upper segment of the aorta, which is known as the isthmus, usually shows a narrowing of variable degree which may be interpreted to indicate the fall in pressure in this

region after most if not all of the aortic blood supply has been drained into the brachiocephalic vessels proximal to the isthmus. In fact it is likely that this physiologic narrowing is the result of this drop in pressure head. Furthermore, the size of the left ventricle and of the ascending portion of the arch, and the tapering from then on until the isthmus is reached suggest that these structures form a functional as well as anatomic unit. Beyond the isthmus, the descending aortic arch in the region of entrance of the ductus arteriosus becomes a much wider vessel corresponding in size not to the upper aortic segment above but to the wide main pulmonary trunk and the ductus arteriosus. In fact the main pulmonary trunk, ductus arteriosus and lower aortic segment appear anatomically as a single curved vessel which forms an anatomic and functional unit.

More direct evidence of the distinctness of the upper and lower aortic segments is provided by the recent studies of Barclay and his associates (11). These observers injected radiopaque material into the superior and inferior venae cavae of sheep fetuses and followed the course of the injected material by roentgen-ray cinematography. Corresponding to the circulation as described above, they observed that the material injected into the inferior vena cava flowed mainly through the foramen ovale to the left chambers of the heart, thence to the ascending aorta, the coronary and brachiocephalic vessels. The material injected into the superior vena cava coursed through the right chambers of the heart, the pulmonary trunk and thence almost entirely through the ductus arteriosus and the descending aorta.

Additional confirmation of the functional separation of the upper and lower aortic segments is seen in the occasional cases of congenital heart disease in which the separation of the two segments is anatomically as well as functionally complete. Thus in Case 11 of Bonnet (1), there was complete atrophy of the isthmus (distal portion of upper segment). The sole possible source of blood supply to the descending aorta (lower segment) was the pulmonary artery by way of the ductus arteriosus. Abbott (12) collected 5 cases in infants and children in which a hypoplastic arch of the aorta gave off 3 main vessels to the head and upper extremities but had no anatomic continuity with the descending arch, and Evans (10) reported 3 similar cases of anatomic separation of the upper and lower segments. In all of the cases the left ventricle supplied the upper aortic segment and brachiocephalic vessels, while the right ventricle supplied the lower aortic segment through a widely patent ductus arteriosus. These cases indicate that in rare and extreme instances the functional separation of the upper and lower aortic segments may be represented by complete anatomic separation. In such instances, instead of the normal postnatal establishment of a continuous circulation in the upper and lower segments, the fetal functional separation is retained after birth.

The relationship of these two aortic segments to the pathogenesis of

aortic coarctation will be discussed after consideration of the mechanism of the closure of the ductus arteriosus. But it may be noted here that when coarctation of the aorta occurs in any portion of the aortic arch above the attachment of the ductus arteriosus it lies in the upper aortic segment whatever its exact site, degree or extent. On the other hand, constrictions of the aorta at or just below the attachment of the ductus arteriosus lie in the lower aortic segment. Thus an aortic constriction which lies only a centimeter above the attachment of the ductus is in a distinctly separate circulatory unit from a constriction situated at or just below the ductus. The development of these two constrictions of almost identical location may therefore depend on different dynamic factors.

CLOSURE OF THE DUCTUS ARTERIOSUS

Since Kilian's (13) suggestion in 1826, we have come to believe that closure of the ductus arteriosus results from a reduction in pressure in that vessel. This fall in ductus pressure results from the shunting of blood through the pulmonary arterial branches to the lungs as the latter become functioning organs at the time of birth. The fall in ductus blood pressure enables its strong muscular fibers to approximate the walls, and the state of disuse results in a secondary subendothelial proliferation which eventually converts the ductus into a fibrous cord (Klotz (8)). The ductus contains relatively little elastic tissue which might tend to retain patency of the lumen.

Persistent patency of the ductus arteriosus may be the result of two general types of abnormality. Either the pulmonary arterial pressure is normal at birth but failure of the lungs to expand adequately causes only a relatively small drain of the pulmonary blood supply so that a sufficient pressure remains in the ductus arteriosus to keep that vessel open. Or due to associated abnormalities, such as auricular or ventricular septal defects, the pressure in the main pulmonary artery is so elevated to begin with that even when some of the pulmonary blood flow is shunted to the lungs at birth, a sufficient pressure is left to maintain patency of the ductus arteriosus.

In the former event, of course, the lungs in most cases do expand properly after a variable period of weeks or months. But during this critical period the pressure in the left ventricle and upper segment of the aorta is rising and eventually exceeds that in the pulmonary artery. If the circulation in the lungs is insufficiently expanded so that the ductus is still open when the aortic pressure exceeds that on the pulmonary side of the ductus, the latter remains permanently open. For now patency is maintained by a flow from the aorta even though the lungs become normally expanded and the pulmonary pressure falls.

When the ductus closes normally, the lower segment of the aorta, which

during fetal life received its blood from the main pulmonary artery by way of the ductus, must now receive blood from the upper segment of the aorta. This requires an increase in blood pressure and blood flow from the left ventricle through the upper aortic segment in order that the lower half as well as the upper half of the body may be supplied. The increase in blood flow is effected by the passage of the pulmonary arterial blood through the lungs and pulmonary veins to the left atrium and thence to the left ventricle instead of through the ductus and lower aortic segment. Whether or not our assumption is correct that there is little or no blood passing in fetal life from the region of the aortic isthmus above the ductus arteriosus to the lower aortic segment, it is certain that much more blood must traverse this passage in order to maintain a blood supply to the lower half of the body when the ductus closes. This increase in blood flow from the upper aortic segment is necessary to keep the lower aortic segment patent at that point at which the ductus arteriosus is attached. Were there no considerable flow from the upper to the lower segment at this point, the drop in ductus pressure at birth would have the same effect in the adjacent area of the lower aortic segment as in the ductus, producing collapse of the aortic walls and constriction of the aorta.

PROPOSED THEORY OF PATHOGENESIS OF COARCTATION OF AORTA

Developmental basis of aortic coarctation. There seems to be no doubt that the upper segmental, supraductus or so-called infantile form of aortic coarctation is the result of a prenatal abnormality in development. The chief basis for this belief is the great frequency of associated major cardiac anomalies, such as defects of the auricular and ventricular septum, transposition of the great vessels, bilocular and trilocular hearts. The structures involved in these anomalies are formed in the second month of uterine life, so that it may be assumed that the aortic coarctation occurs at the same time. Abbott (14) found that of 82 cases of coarctation of the aorta in infants under 1 year of age, 50 were complicated by grave or major cardiac anomalies and 19 by minor ones. There were 15 uncomplicated cases, but it must be emphasized that some of the cases in infants under 1 year of age were undoubtedly examples of lower segmental, i.e., adult coarctation of the aorta, with premature death from unrelated causes. Furthermore, the finding of upper segmental aortic constriction (infantile coarctation) in the newborn and in fetuses is additional evidence that the anomaly is one of relatively early intra-uterine life. This anomaly is caused probably by a defect in the development of the fetal left fourth aortic arch which is represented later by the upper aortic segment running from the left ventricle to the site of attachment of the ductus arteriosus.

The evidence for an antenatal developmental abnormality as the basis of the lower segmental or adult type of coarctation of the aorta is less

convincing although significant. Thus despite the absence in undoubted cases of adult coarctation of the grave cardiac anomalies which complicate the infantile form, there are numerous minor anomalies, particularly those of the aortic arch, which suggest that the adult as well as the infantile coarctation is the result of an antenatal developmental abnormality. Abbott (14) found that in 155 cases of aortic coarctation in subjects over 1 year 57 were associated with minor anomalies, 86 were uncomplicated and 13 were combined with grave anomalies. But these 13 proved to be either cases of the infantile type despite survival beyond 1 year of age, or cases without significant coarctation. The specific minor anomalies included bicuspid aortic valves and subaortic stenosis, but especially abnormal origin or distribution of branches of the aortic arch. Since the involved structures are formed in early uterine life, it may be considered that the associated adult coarctation is related in some way to these early developmental abnormalities.

In particular, Abbott was impressed by a case of adult coarctation reported by Blackford (15) in which there was a persistence of a right dorsal aorta arising from a costocervical trunk of the aortic arch and connecting with the descending aorta below the closed ductus arteriosus. There was also a similar case reported by Hamilton and Abbott (16) of an anomalous vessel, probably representing a persistent left fifth aortic arch, which ran from the aorta above the closed ductus to a mass of enlarged glands on the right side of the arch where it was lost. It seemed likely that both the coarctation and the anomalous vessels developed in the second month of fetal life when the aortic arches are being transformed into their adult types.

Despite this evidence for the developmental origin of the adult as well as the infantile coarctation, it remains to be explained why the adult coarctation, unlike the infantile is not found in fetuses or the newborn, why it is so closely approximated to the site of attachment of the ductus arteriosus and why most if not all of the reported cases are associated with closure of the ductus arteriosus. I believe that the prenatal developmental anomalies are the primary basis of the adult as well as of the infantile form of aortic coarctation, but that the type which is encountered depends entirely on whether the ductus remains patent or closed.

RELATION OF PATENCY OR CLOSURE OF THE DUCTUS TO TYPE OF COARCTATION

Upper segmental (infantile) coarctation. The infantile type of aortic coarctation has almost always been associated in reported cases with patency of the ductus arteriosus (fig. 3). If classification of a case of coarctation as infantile is made on the basis of location of the constriction in the upper (supraductus) aortic segment instead of on the basis of age, and if the constriction is distinct, there are no definite exceptions to patency

of the ductus arteriosus. The association is not accidental, but is based on the following developmental factors:

1. If the aortic constriction is extreme such as in certain cases of atresia of part of the arch, the blood pressure and blood flow in the upper aortic segment remains relatively small while that in the main pulmonary artery is correspondingly high. Opening of the pulmonary circulation with the development of pulmonary respiration causes a fall in pressure insufficient to effect closure of the ductus arteriosus. The incomplete or complete obstruction to blood flow from the upper to the lower aortic segment is compensated quantitatively by blood flow from the pulmonary artery and ductus arteriosus although this blood is qualitatively deficient in oxygen.

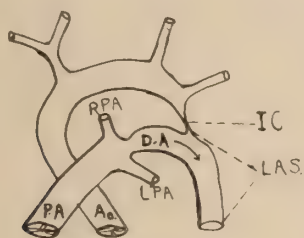


FIG. 3

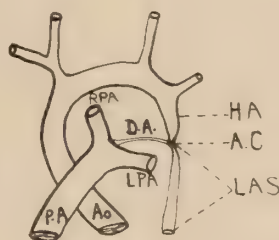


FIG. 4

FIG. 3. Upper segmental (supraductus or infantile) aortic coarctation (IC). Ductus arteriosus (DA), patent as in fetal circulation, supplies lower aortic segment (LAS).

FIG. 4. Lower segmental (adult) aortic coarctation (AC) at or just below ductus insertion, early weeks postpartum. Ductus arteriosus (DA) closed. Prenatal congenital hypoplasia of aorta (HA) with failure to increase blood flow postpartum to lower aortic segment. Coarctation due to drop in blood pressure in region of closed ductus.

2. As a rule, upper segmental (infantile) aortic coarctation is associated with grave cardiac anomalies. Such association is common in congenital cardiovascular anomalies because the same disturbance which causes one defect is likely also to interfere with the proper development of neighboring structures. When upper segmental aortic coarctation and grave cardiac anomalies are combined, patency of the ductus is a constant feature. This is due to the fact that the anomalies usually associated, i.e., interventricular and interauricular septal defects, result in an abnormally high right ventricular and main pulmonary arterial pressure at birth. This is accentuated by the upper segmental aortic constriction, which interferes with increase of blood flow through the upper aortic segment. Thus the development of pulmonary respiration and a pulmonary circulation does not reduce the pressure in the ductus arteriosus sufficiently to permit closure and obliteration of this passage.

3. Patency of the ductus arteriosus is an integral feature in the occur-

rence of infantile coarctation, but not of adult coarctation, for as will be shown under the next heading the adult (lower aortic segmental) type of coarctation cannot occur if the ductus remains open.

The above explanation binds the association of the cardinal features of the upper segmental (infantile) type of aortic coarctation, namely the location of the constriction above the site of attachment of the ductus, the associated grave cardiac anomalies and patency of the ductus arteriosus. Other features are secondary. The unfavorable prognosis, with death usually in early infancy, is due chiefly to the serious nature of the cardiac anomalies as well as to the coarctation itself. Whichever of the above mechanisms accounts for patency of the ductus in a given case, the flow of blood is from the pulmonary artery to the aorta because of the higher pressure in the former. Therefore, a high arterial oxygen unsaturation and cyanosis are the rule. This contrasts with the adult forms of coarctation, in which the collateral circulation passing the obstruction brings oxygenated blood to the lower half of the body. Finally, the absence of such a collateral circulation in cases of upper segmental (infantile) coarctation is due to persistence of a patent ductus arteriosus which maintains a blood flow to the lower segment of the aorta. Rarely it is possible for a collateral circulation to appear in upper segmental (infantile) aortic coarctation if the ductus does not provide an adequate blood supply to the lower segment (Ulrich's case 3 (17)).

Lower segmental (adult) coarctation. The evidence suggesting a primary prenatal developmental anomaly in the cases of adult as well as infantile coarctation has been noted above. The theory here proposed assumes that this anomaly, like that in infantile coarctation, originally concerns the upper aortic segment. The general feature of the primary defect is the failure of development, after birth, of an adequate blood pressure and blood flow in the aortic isthmus just above the entrance of the ductus arteriosus. This may be due to a congenital hypoplasia of the aortic arch, a constriction of the arch, or the shunting of blood by an anomalous vessel from the upper segment before it reaches the aortic isthmus.

But unlike infantile coarctation, there is no complete atresia or severe constriction which raises the right ventricular and main pulmonary arterial pressure sufficiently to keep the ductus arteriosus open. Nor do the cases of adult coarctation have associated cardiac anomalies of the septa or great vessels, which might have the same effect of maintaining patency of the ductus. Therefore, despite a defect in the upper aortic segment the ductus arteriosus undergoes its normal drop in blood pressure and its normal closure after birth. But the upper aortic segment which normally takes over the supply of blood to the lower aortic segment when the ductus closes is hypoplastic or constricted because of an early developmental anomaly. The normal rise in pressure and growth fails to occur. Therefore, the fall in pressure, occurring in the ductus arteriosus, affects also

the immediately adjacent portion of the aorta into which it empties and the vicinity immediately below (i.e., the lower aortic segment) (fig. 4). If the deficiency in upper aortic blood supply is great enough then the same drop in pressure which leads to closure of the ductus arteriosus leads to extreme or moderate constriction of the immediately adjacent lower aortic segment, which at this stage is really a continuation of the ductus arteriosus.

An essential feature of this theory is that closure of the ductus arteriosus is not a common and accidental association of the adult form of coarctation, but a necessary prerequisite and cause. According to Abbott (14), closure of the ductus arteriosus is present in 90 per cent of the reported cases. The remaining 10 per cent of cases of presumed adult aortic coarctation with patent ductus arteriosus would seem to invalidate the theory. I have been unable to find the original reports of all the so-called cases of adult coarctation of the aorta with patent ductus arteriosus. But in all the cases in which I have been able to check the original data, I have found either that 1) they were really cases of *infantile* coarctation which survived beyond the first year of life, or 2) that the location of the constriction was definitely above the origin of the ductus, which would make it a case of the infantile type, or 3) that the site and type of constriction is not clearly stated.

Although closure of the ductus arteriosus is described as the determining cause of the adult type, it is clear that this is not the primary cause or else closure of the ductus would in itself more frequently if not always produce a coarctation. The primary cause is the developmental disturbance in the upper aortic segment which prevents an adequate maintenance of pressure in the juxtaductal portion of the lower aortic segment just after birth when the ductus becomes occluded.

APPLICATIONS OF THE PROPOSED THEORY

The application of this theory to the infantile form of coarctation has been briefly discussed above. Since the developmental origin of this type of coarctation is generally accepted, detailed discussion is unnecessary. It is merely emphasized that according to the theory proposed the association of grave anomalies and of a patent ductus arteriosus are not mere coincidences, but are determining factors in the persistence of the infantile type. Thus in most instances it is the existence of these associated anomalies which determine the abnormal pressure relationships which maintain the patency of the ductus.

In this connection it must be explained why, in cases of adult coarctation, the infantile hypoplasia or constriction of the upper aortic segment, which is the primary lesion, is not found simultaneously with the adult coarctation lower down in the aorta, at or below the entrance of the ductus arteriosus. As a matter of fact it has long been known that hypoplasia of the aorta and

varying degrees of narrowing of the upper segment, especially in the region of the isthmus, are found with surprising frequency in cases of adult coarctation. This was never understood, since in most instances the aortic arch is dilated and the left ventricle hypertrophied. That hypoplasia or constriction of the upper aortic segment is not seen more frequently may be understood from the secondary affects of adult coarctation, which develop over a period of years. Thus, through mechanisms still imperfectly understood, hypertension and left ventricular hypertrophy eventually appear. This, probably in combination with the congenital weakness of the upper aortic segment, which is part of the primary defect, eventually results in distention of the upper aorta, so that the original constriction is no longer visible. The incidence of rupture of the aorta in adult coarctation, which is out of all proportion to that in noncoarctation cases with similar blood pressures, is added evidence of a congenital defect of the upper aortic segment. Finally it remains to be determined whether careful observation of the distal portion of the upper segment of the aorta in cases of adult coarctation may not reveal even more instances of the primary defect in that segment.

The proposed theory harmonizes the evidence for a prenatal developmental anomaly in both types of coarctation of the aorta and the observations connecting the adult type with closure of the ductus arteriosus. The developmental anomaly of the upper segment is the primary defect, but the superimposed effect of closure of the ductus accounts for the location of the stricture at or below the ductus attachment to the aorta. The explanation offered also accounts for the fact that this type of constriction is never found in fetuses or the newborn, that is, before the ductus is closed.

The proposed theory for the pathogenesis of adult coarctation may be applied satisfactorily to the cases of Blackford (15) and of Hamilton and Abbott (16), in which vestiges of the right dorsal aorta or left fifth aortic arch, respectively, persisted as anomalous vessels which shunted blood from the upper aortic segment before it reached the aortic isthmus. It is indeed true that these abnormalities must have occurred in the second month of fetal life when the aortic arches assume their adult form, but it need not be concluded, as by Abbott, that the adult infraductal coarctation also occurred at the same time. Thus, these anomalous shunts served to short-circuit blood from the upper aortic segment above the ductus and isthmus to the lower segment below the ductus so that the blood flow and the blood pressure in the supraductal region of the isthmus was quite low. When the ductus arteriosus was closed, as occurred in both these cases, there was no adequate compensatory increase in blood flow from the isthmus past the region of entrance of the ductus, due to the anomalous shunt. This juxtaductal area in the lower aortic segment therefore must have collapsed and developed a constriction at the time when the ductus closed. As a matter of fact, in the case of Hamilton and Abbott (16),

it is clearly stated that the isthmus above the coarctation was also markedly narrowed, an anatomic expression of the low blood pressure in that region.

Subaortic stenosis, itself a very uncommon lesion, is found in cases of adult coarctation of the aorta with more than coincidental frequency. It may be that such a lesion in fetal life may have an effect similar to narrowing or hypoplasia of the upper aortic segment beyond it. The presence of a subaortic stenosis may prevent the usual increase in blood pressure and blood flow through the upper aortic segment which normally prevents constriction of the aorta in the region of the ductus when the latter becomes occluded.

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THERAPEUTIC AGENTS AND RENAL IMPLANTATIONS IN EXPERIMENTAL HYPERTENSION¹

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Many different drugs and diets have been advocated for the purpose of reducing blood pressure in patients with hypertension. Clinical trials have usually resulted in widely conflicting reports. A decline in pressure ascribed to drugs could often be reproduced by means of placebos and reassurance. Ayman (1), Fishberg (2), and Evans and Loughnan (3), among others, have emphasized the spontaneous variations and emotional factors to be considered in evaluating the efficacy of therapeutic measures in human hypertensives.

The experimental animal lends itself to tests comparatively free of disturbing psychic influences. Observations in laboratory animals have awaited the introduction of methods for inducing sustained hypertension resembling that seen in human subjects. Davis and Barker (4) used hypertensive dogs and noted a decline in blood pressure following administration of cyanates. Grollman, Harrison and Williams (5) recently tested various therapeutic procedures in rats made hypertensive by means of subtotal nephrectomy. There is some evidence which suggests that the mechanism in this type of hypertension may differ from that due to limitation of blood flow to the kidney (6, 7). In the present study we induced hypertension in rats by means of renal ischemia due to cellophane (8). Sustained hypertension frequently follows operation on one kidney, the opposite kidney remaining intact (9). Hypertension from this type of injury arises from a combination of factors, obstruction of the renal pedicle, prevention of collateral circulation through the capsule, interstitial nephritis, and renal compression by the fibrous perinephritic mass.

The therapeutic agents studied include erythrol tetranitrate, bismuth subnitrate, potassium thiocyanate, garlic extract (*allium sativum*) and a preparation of desiccated kidney substance (nephritin).²

Page and his co-workers (10) were able to prepare renal extracts containing a substance which lowered blood pressure in hypertensive dogs and rats and in patients with hypertension. We have tested this extract in six rats.

Magnesium salts have been reported to have depressor actions in pa-

¹ This study was aided by a grant from the Lionel Sutro Fund.

² A generous supply of this material was provided by Reed Carnick & Co.

tients with acute glomerular nephritis (11) and in rats made hypertensive by injection of ergotamine tartrate (12). It seemed of interest to study the action of these salts in chronic renal hypertension.

Rodbard, Katz and Sokolow (13) noted reduction in blood pressure following subcutaneous implantation of normal kidney tissue in Goldblatt dogs. Liver, spleen and boiled kidney tissue produced either transient or no decline in pressure. Goldblatt and Kahn (14) did not confirm these findings when precautions were taken to prevent infection.

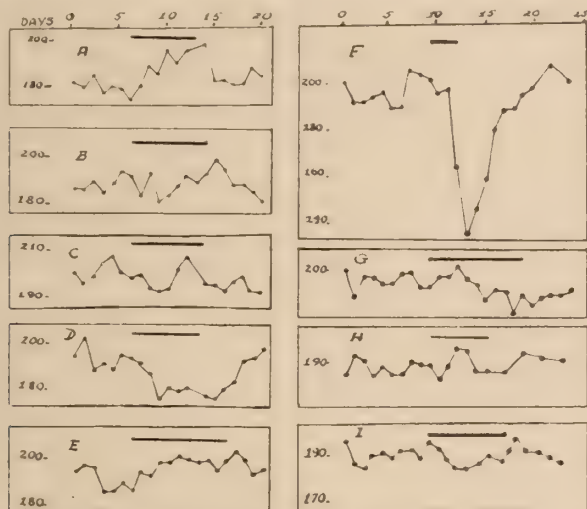


FIG. 1. Test of various substances on the blood pressure of hypertensive rats. Each curve represents the average values in 6 to 8 rats. Substances tested were given for variable periods denoted by the heavy line above the curves. The ratio of the dose administered to that generally recommended for use in humans in proportion to body weight is recorded in the parenthesis for each substance as follows:

Curve A, erythrol tetranitrate, 0.05 gram per day (30x); curve B, allium sativum, 0.5 to 1.0 gram per day (100x); curve C, potassium thiocyanate, 0.1 gram per day (25x); curve D, potassium thiocyanate, 0.2 gram per day (50x); curve E, desiccated kidney tissue, 0.4 gram per day (30x); curve F, renal extract (page), 0.5 cc. per day; curve G, magnesium carbonate, 0.2 gram per day; curve H, magnesium sulphate, 0.05 gram per day; curve I, bismuth subnitrate, 0.075 gram per day (10x).

In the present reports we have included some observation on tissue implantations in rats.

METHODS

Hypertension was induced in rats by wrapping one or both kidneys in heavy cellophane. Systolic blood pressures were determined without anesthesia using the methods of Williams, Harrison and Grollman (15). All of the test animals had had hypertension (elevation of blood pressure of at least 40 mm. of mercury above the pre-operative level) for a period of not less than 6 months. Daily pressure readings were made prior to and during the trial period.

Oral medication in the desired dosage was mixed with a limited daily food supply so that the total amount was consumed each day. Magnesium sulphate and the renal extract were given subcutaneously.

Tissues for implantation were taken from freshly killed stock rats, sliced into flat strips and about 1.5 to 2 grams embedded in subcutaneous tissue over the abdomen. Iodine and alcohol were used for the skin, but strict

TABLE 1

Effect of subcutaneous implantations of various tissues on blood pressure of hypertensive rats

RAT NUMBER	TISSUE IMPLANTED	MEAN SYSTOLIC PRESSURE BEFORE IMPLANTATION	MAXIMUM CHANGE* IN PRESSURE AFTER IMPLANTATION	DURATION† OF CHANGE
		mm. Hg	mm. Hg	Days
1	Kidney	164	-10	2)
2	Kidney	190	0	0
3	Kidney	172	+20	8
4	Kidney	187	0	0) no abscess
5	Kidney	178	0	0)
6	Kidney	172	+16	3
7	Kidney	213	0	0)
8	Kidney	185	-65	20
9	Kidney	203	-43	4
10	Kidney	200	-28	5
11	Kidney	193	-15	6) abscess present
12	Kidney	199	-35	6
13	Kidney	165	-21	4
14	Kidney	186	-34	12)
15	Spleen	180	0	0 no abscess
16	Spleen	197	-21	4)
17	Spleen	187	-25	4) abscess present
18	Spleen	172	-36	3)
19	Liver	172	0	0 no abscess
20	Liver	195	-31	5
21	Liver	192	-22	4) abscess present
22	Liver	184	-28	6)

* Changes of less than 10 mm. Hg from the mean value are recorded as 0.

† Days required to return to the mean value.

aseptic technique was not employed. The necrotic mass which frequently formed was allowed to heal spontaneously.

RESULTS

The results of the various tests are illustrated graphically in Figure 1. Each curve represents the average values for 6 to 8 rats. No reduction in pressure occurred with erythrol tetranitrate (A), allium sativum (B), mag-

nesium salts (*G* and *H*), desiccated kidney substance (*E*) or bismuth subnitrate (*I*). Potassium thiocyanate in doses of 0.2 gram daily caused a slight but definite decline in pressure in 7 out of 8 animals (*D*). One of these died and several became weak and inactive. Magnesium carbonate and bismuth subnitrate both caused considerable diarrhea and weight loss but no change in blood pressure. All rats receiving the Page renal extract showed a decline on the fourth day of treatment which continued for one day after treatment was stopped, returning gradually to the original level (*F*). Subsequent readministration of the extract was again accompanied by a decline in pressure almost to the prehypertensive level. The animals appeared normally active and healthy throughout this period.

Changes in pressure following tissue implantation are recorded in Table I. Changes of less than 10 mm. of mercury from the mean pressure were not considered significant. Fourteen of the 22 animals showed a significant fall in pressure accompanied in all instances except one (#1) by a local abscess and in most cases by anorexia and inactivity. Depressor effects were noted with liver and spleen as well as with kidney tissue. Although the two greatest declines occurred with kidney tissue, quantitative differences cannot be evaluated in this small series. In general the greater the change in pressure the longer it took to return to the original level. Only one of the nine rats (#1) without a visible abscess showed a fall in blood pressure.

DISCUSSION

Many of the symptoms associated with hypertension have no direct relation to the elevated pressure. Symptomatic improvement often occurs with sedatives, rest and a variety of non-specific remedies (1, 3). Symptomatic relief, however desirable, cannot serve as a criterion for depressor activity. There is considerable disagreement concerning the blood pressure reducing power of various therapeutic measures in patients (2). This may be due in part to emotional factors and differences in degrees of enthusiasm incidental to treatment, factors which are not important in the laboratory animal.

There is increasing evidence that the circulatory disorder induced in experimental animals by limitation of the blood flow to the kidneys resembles closely that seen in patients with so-called essential hypertension (16). Tests of the efficacy of therapeutic agents in laboratory animals are therefore applicable to human hypertensives. Of the substances studied, administered in doses many times greater than that advocated for man, only two possessed detectable blood pressure reducing properties. The hypotensive effect of potassium thiocyanate was definite but slight and was accompanied by signs of toxicity. This is in agreement with the experience of many clinicians (2).

The renal extract was the only substance which reduced the blood pres-

sure to the normal level. Two groups of investigators (17, 18) using different lines of reasoning and working independently had arrived almost simultaneously at preparations which are similar if not identical. The ability of these substances to effectively reduce the blood pressure in patients with hypertension and in hypertensive animals constitutes additional evidence in favor of the similarity of the underlying mechanism in the two conditions.

Our observations in rats with perinephritis agree closely with those of Grollman, Harrison and Williams (5) in partially nephrectomised animals and suggest that the basic factors responsible for the elevation in blood pressure are the same in both types of hypertension. By the same token, the difference in response to magnesium therapy between our animals and those with hypertension due to ergotamine, reported by Rubin and Rapoport (12), points to a possible difference in the mechanism of the elevated tension in the two groups.

The depressor effect of tissue implants in our animals, as in those of Goldblatt and Kahn (14), was not specific for the kidney. It seemed to be correlated with the appearance of a localised necrotic mass, and disappeared with the evacuation of the abscess. Usually the local necrosis together with the fall in blood pressure occurred on the second or third day after implantation. In two instances (rats * 11 and 14) no changes were noted until the seventh or eighth days when both the lesion and the decline in blood pressure appeared simultaneously. If absorption of a specific substance from the kidney were the cause of the hypotensive effect it should have taken place much earlier. A fall in pressure is commonly observed in hypertensive rats and dogs during respiratory and wound infections. In the dog it does not appear to be due to the effect of fever (19). Whatever the mechanism the evidence indicates that the decline in pressure is associated with the presence of inflammation whether local or systemic.

SUMMARY

Studies of the blood pressure reducing properties of a number of "hypotensive" agents and of tissue implantations in rats with chronic hypertension of renal origin indicate as follows:

1. Erythrol tetranitrate, bismuth subnitrate, allium sativum (garlic extract) and dried kidney tissue (nephritin) are without effect. Potassium thiocyanate in doses which, in proportion to body weight, are about 50 times those advocated for man, produce a slight decline in pressure accompanied by evidences of toxicity.

2. Magnesium carbonate and sulphate are ineffective.

3. An extract of kidney (Page) reduced blood pressure to the normal level during the period of administration of the extract.

4. A fall in blood pressure occurs following subcutaneous implantation of strips of tissue taken from the kidney, liver and spleen. The depressor

effect is correlated with the presence of localised necrotic tissue and does not seem to be specific for the kidney.

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SUPPURATIVE TENOSYNOVITIS OF THE HAND

A PLAN OF TREATMENT

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The functional results of the surgical treatment of acute suppurative tenosynovitis of the flexor sheaths of the hand have, until very recently, been far from satisfactory. Even under the most favorable circumstances, such as early operation, proper technique, prevention of secondary contamination and survival of the tendons, functional disability was marked in the majority of cases. In 1924, I reported a series of 460 hand infections, stressing, particularly, the functional results in the various forms of infection. Included in this series was a group of 42 tendon sheath infections that were subjected to careful scrutiny from the standpoint of the ultimate functional result.

I would like to repeat verbatim a paragraph from that article written seventeen years ago, because the remarks made then have particular significance at this time. I have had no reason to change my views as expressed at that time until very recently. The paragraph reads as follows: "I believe that Kanavel's remark, 'in nearly every case an early diagnosis can be made and the function of the hand saved,' is too optimistic. It is agreed that an early diagnosis can and should be made in nearly every case; but it appears that in an appreciable proportion of the cases with optimum conditions present such as early diagnosis, cooperation on the part of the patient and the institution of proper operative and postoperative treatment, some permanent defect in function remains." Among the 42 cases in this group, in only six instances was there restoration of normal function, i.e., 14 per cent of the total.

In the succeeding years, an increasing experience with this disease has not been fruitful of any improvement in the results already described. However, with the advent of sulfonamide therapy, a renewed interest was created and an effort was made to effect a plan of treatment which would materially diminish the functional disability previously associated with this type of infection. This communication is concerned, therefore, with our recent experiences.

About four years ago, a patient was admitted to the hospital with an acute tendon sheath infection of the middle finger which presented such unusual features as to suggest the clinical diagnosis of gonococcal tenosynovitis. Aspiration of the involved sheath with a fine hypodermic

needle yielded a few drops of purulent material which, upon smear, demonstrated intra- and extra-cellular gram negative diplococci, and upon culture, the gonococcus. The patient was not operated upon. Instead, the finger was immobilized in partial flexion, i.e., the position of rest, and the patient was given three hyperthermia treatments. There was a dramatic subsidence of the infection and the patient went on to recovery with restoration of complete function in the finger.

The favorable outcome in this instance suggested, with the advent of the sulfonamide drugs, an extension of this method of therapy for infections of the flexor sheaths caused by other pyogenic organisms. Since then five patients have been treated by the method to be described and the functional results have been so uniformly favorable that I have no hesitancy in recommending it as the procedure of choice in all cases of suppurative tenosynovitis of the hand.

The survival or death of the flexor tendons during or following a suppurative infection will depend on a number of factors. First and foremost, is the duration of the disease before the patient seeks treatment. Experience has shown that if the infection has been present for more than 24 hours, the chance of survival of the tendons will be very little indeed. Second, the degree of tension within the sheath by inflammatory products will be the deciding factor in obliterating the precarious blood supply of the tendons. And third, as I indicated in 1924, the introduction of secondary contaminating organisms after operative drainage of the flexor sheaths will greatly increase the risk of tendon necrosis. Any method of therapy must take cognizance of these three factors. Other factors beyond the control of the surgeon are the degree of virulence of the infecting organism and the resistance of the patient.

With the method advocated, the surgeon must take into account the duration of the illness, the degree of tension in the sheath as evidenced by the extent of swelling of the finger, palm and dorsum of the hand and the identity of the infecting organism. If the disease is less than 24 hours old, the sheath is aspirated under aseptic precautions and as much material as possible is removed. Smears and cultures are made in order to quickly identify the organism. Sulfonamide therapy, preferably by the intravenous route, is immediately instituted. If tension and swelling in the involved part is only moderate, no operation is done. Instead, the finger is immobilized in partial flexion, the position of rest. Wet dressings or hot soaks may or may not be used. I believe that wet dressings probably make for the patient's comfort. If there is great swelling of the finger and obvious increased tension within the sheath, operation should be performed. This should consist of lateral incisions made in a bloodless field, with multiple small incisions in the tendon sheath. No drain of any sort should be inserted in these incisions. After a light dressing is applied, the finger is immobilized on a sterile metal splint in partial flexion and the hand and

forearm are carefully wrapped in sterile towels. The dressings should not be disturbed for three or four days. During this period, sulfonamide therapy is continued. At the first dressing, the surgeon will be agreeably surprised with the appearance of the wounds. Whereas, formerly the wounds presented an unhealthy soggy appearance with purulent discharge now they appear dry and firm. Healing takes place quickly. Because of the absence of pain, early effective active motion may be started. The rapid return of function has been particularly noteworthy.

In the five cases cited above, operation was performed in three instances. A hemolytic streptococcus was cultured in four cases and a staphylococcus aureus in one. In the four patients infected with the streptococcus, there was return of complete function. In the fifth patient, there is some limitation of flexion, but the finger is serviceable.

The functional results obtained in these five consecutive cases of suppurative tenosynovitis of the hand, are, in my experience, unique. The method advocated in this report, therefore, merits more extended use.

PROPHYLACTIC IMPLANTATION OF ESTROGENS FOLLOWING SURGICAL AND RADIUM CASTRATION

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The studies of numerous investigators have established the fact that the ovaries, in addition to performing the function of ovulation, play a very important role in the normal endocrine balance of the female. It has been shown that the ovaries produce the sterol sex hormone, α -estradiol, which regulates the production of gonadotropic hormone by the hypophysis and stimulates proliferation of the epithelial and muscular elements of the mullerian tract, and also acts as a stabilizer of the autonomic nervous system. It has furthermore been demonstrated that following the removal of both ovaries, the hypophysis becomes hyperactive (1, 2, 3, 4, 5), producing excessive amounts of gonadotropic hormone, which can be detected in the blood and urine. Ovariectomized women furthermore develop a progressive atrophy of the genital tract (6, 7) and manifest a wide variety of symptoms. Recent studies (8) have shown that the hyperactivity of the hypophysis can be detected in some individuals as early as three days after the removal of the ovaries.

The rationale of estrogen therapy in the treatment of the menopause syndrome is firmly established. Thus, it has been shown that by the administration of adequate amounts of estrogens, the hyperactivity of the hypophysis can be inhibited (9, 10, 11, 12), atrophy in the genital tract can be corrected (13, 26), and the varied clinical manifestation of autonomic imbalance resulting from the estrogen deficiency can be relieved. In view of the demonstrated effectiveness of estrogens in restoring the normal pituitary-ovarian balance and their efficiency in relieving the menopausal symptoms, it seems logical to attempt to prevent the estrogen deficiency and its concomitant somatic and psychic disturbances by prophylactically administering estrogens to patients at the time of removal of both ovaries (14).

The subcutaneous implantation of estrogens affords us an ideal method for this purpose by providing a steady source of estrogens for a relatively long period of time. The efficiency of this method of administration of estrogens has been demonstrated in animals (15, 16), and its therapeutic effectiveness in the treatment of the menopause proven in a series of over 150 cases which have been implanted during the past two and a half years

(17, 18, 19). The practical therapeutic value of estrogen implantation has been confirmed by several investigators.

Our studies show that following the single implantation of α -estradiol crystals the excessive urinary gonadotropic hormone excretion in ovariectomized women can be inhibited for as long as 5 months (19, 20); estrogenic effects in the endometrium and vaginal mucosa are demonstrable for many months (18); and the menopausal symptoms can be relieved for periods varying from 4 months to 2 years (22). In a preliminary report we described very satisfactory results in a series of 36 cases implanted prophylactically. Here we wish to present the results of an augmented series, including several patients who had been treated with radium.

Methods and materials. The 50 implantations were performed on 46 selected patients from the ward service who required bilateral ovariectomy. The indications for operation were variable and included fibroid uteri, ovarian tumors (benign and malignant), carcinoma of the uterus, and chronic adnexitis. The range in age was 25 to 52 years, the majority of patients being 40 to 45 years of age. The implantations were usually performed on the day of operation or several days thereafter. Four patients in this group required reimplantation because of the onset of menopausal symptoms. Three implantations were performed on patients who received intra-uterine radium therapy for metrorrhagia associated with fibroids.

Hormone and dosage. Pellets and loose crystals of chemically pure estrogenic hormone were used in this study. The technique of the implantation has been described elsewhere (17). The implanted material consisted of loose crystals or compressed pellets of estradiol and estradiol benzoate and estrol dipropionate. The total dose in each case varied from 15 mg. to 35.8 mg. of the hormone.

Results. The ability of the implantation to prevent the onset of hot flashes was employed as a measure of the therapeutic efficiency of the procedure.

In this series of cases the implantations were well tolerated under the skin, and in no instance was there evidence of infection or a spontaneous extrusion of the pellets or crystals. These patients have been observed since implantation for periods of time varying from 3 months to 28 months. The majority of the patients have been followed for more than 9 months.

None of the patients, with one exception, experienced hot flashes for the first 3 months post-implantation. During the following 3 months some of the patients began to have occasional weak flashes which in the majority did not increase in frequency or severity. Approximately 50 per cent of the patients experienced no flushes during the period of time under observation.

Thirteen patients have required additional estrogenic therapy because of the onset of menopausal symptoms at periods varying from 3 to 11 months after the implantation. Four of these patients have been reimplanted and at present are again asymptomatic.

DISCUSSION

The above results are difficult of evaluation without some knowledge of the incidence of menopausal symptoms in untreated patients following bilateral ovariectomy.

We have found that in a series of 88 untreated ovariectomized women (14) 26 per cent developed symptoms within one week following bilateral ovariectomy; 42 per cent within 2 weeks; and 89 per cent within 12 weeks. These results stand in sharp contrast to the results in the implanted cases. None of the latter group (with the exception of 1 patient, who developed flushes 6 weeks following implantation) experienced symptoms during the first 3 months after implantation. The 3 patients with radium induced climacteric require special mention. Each of these patients was implanted with approximately 17 mg. of α -estradiol crystals. They have been observed for 3 months and have been asymptomatic and no uterine bleeding has occurred. Previous (22) experience with the implantation of estrogens in cases of spontaneous menopause has shown that the implantation of crystals of α -estradiol in amounts varying from 25 to 30 mg. will induce uterine bleeding in more than 50 per cent of the patients, whereas in patients implanted with 4 to 10 mg. of α -estradiol no bleeding is induced. It was also noted that the tendency to bleeding following implantation of estrogens in patients months or years after x-ray or radium induced castration is much less than in patients following the natural menopause. The indication for the use of radium is usually excessive uterine bleeding. Therefore, if estrogens are to be used prophylactically, smaller doses should be employed. The dose used in these cases should be between 15 and 20 mg. It would appear that theoretically it is possible to prevent the onset of menopausal symptoms indefinitely by repeated prophylactic implantations of estrogens.

This study has demonstrated the feasibility of preventing the occurrence of the menopausal syndrome after bilateral ovariectomy or radium castration by the single procedure of prophylactic estrogen implantation.

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INTRACRANIAL ANEURYSMS

THEIR ORIGIN AND CLINICAL BEHAVIOR IN A SERIES OF VERIFIED CASES

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Intracranial aneurysms are no longer regarded as interesting display specimens. They now, not infrequently constitute a diagnostic problem both for the neurologist and the general practitioner. Since the advent of surgical intervention as a promising therapeutic measure, it becomes obvious that there is great need for their earlier clinical recognition and precise localization. This in turn calls for a thorough investigation of the cause and the varied clinical and anatomical behavior of this vascular anomaly if better leads are to be had for the establishment of its presence, its location and adaptability to surgical treatment. To meet this demand, the results of a fairly large number of pathological and clinical studies of verified or otherwise identified intracranial aneurysms are now available (1 to 6). To further serve this purpose, we submit our account of clinical and anatomical findings in a selected series of aneurysms of cerebral arteries.

In the choice of the selected cases, we were guided by a desire to present the somewhat less well known clinical manifestations and an anatomical behavior less commonly encountered in intracranial aneurysms.

A brief survey of the known data pertaining to the etiology of cerebral aneurysms discloses that the weight of evidence favors the view that in the majority of instances, aneurysms of cerebral arteries are to a great extent the result of an acquired pathologic process in the affected area of the involved vessel. MacDonald and Korb (7) surveyed 1125 cases assembled from the literature, and found that there were 572 cases in which the larger cerebral arterial trunks were satisfactorily described. Of these, 67.3 per cent disclosed pathologic changes in the cerebral vessels in addition to the aneurysmal formations. In 49.5 per cent of the total number of cases in which the vessels were found to be diseased, the pathologic process was that of arteriosclerosis. Thus, this thorough and timely analysis by MacDonald and Korb points to the predominance of arteriosclerosis as a cause for this abnormal focal vessel distension. This is confirmed by Tuthill (8) who called attention to splitting and reduplication of the internal elastic lamella at the bifurcation of the cerebral arteries undergoing arteriosclerotic changes.

Inflammatory alterations also hold a prominent place in the causation of

aneurysms but only second to those of degeneration (arteriosclerotic). Impaction by infected emboli from an ulcerating endocardium and metastatic infections involving the inner layer of the affected vessel are common. Such disease processes usually undermine the elasticity and resilience of the vessel wall which eventually yields to the pressure of the blood stream and gives rise to what is called a mycotic aneurysm (9, 10, 11).

It is rather surprising to find that syphilis plays a minor rôle as an etiologic factor in cerebral aneurysms. Many investigators are in accord with this observation (12, 13). Recently, Maass (14) concluded that syphilis was the most common cause of intracranial aneurysm. However, his observations on eight cases of cerebral aneurysm are not too convincing.

The rather high incidence of normal arteries among instances of proven aneurysmal formations is significant. It seems to support the view held by many that an inherent factor exists in the nature of a congenital structural defect in affected blood vessels, predisposing them to focal saccular distension. Eppinger (15) as far back as 1887 called attention to this defect at the bifurcation of the cerebral arteries as an antecedent cause for aneurysmal formation. This would seem to find support in the frequent occurrence of aneurysms in the young without there being any evidence of embolization or degenerative disease. Others have adopted and modified this view, among them Forbus (16). More recently Forbes (17) found in children a defective development in the muscular coat of the superficial blood vessels of the brain. This defect was at the point of their bifurcation, and where he considered the arterial pressure to be greatest. He regarded them as "weak spots" similar to those present in vessels in instances of cerebral aneurysm. To some, the evidence so far presented in support of this view may not be convincing; nevertheless, it is quite obvious that these observations are in accord with the probability that both the inherent "weak spots" and the superimposed acquired pathologic process are complementary factors in the production of aneurysm. These findings lend support to the old concept of the "*locus minoris resistentiae*". Trauma is another etiologic factor which may be added to those already mentioned. It also operates as a provocative agent superimposed on a preexisting defect in the vessel wall.

The diagnosis of intracranial aneurysms is a problem which invites a few remarks that will serve the immediate purpose of this report. It calls for an enumeration of the more characteristic clinical manifestations of cerebral aneurysms, and leads to a brief consideration of several phases in the behavior of these vascular expansions. First, it must be recalled that this type of expanding lesion defies detection in the early stages because of its inherent quality of slow development. No symptoms or signs pointing to its existence present themselves until the vessel wall gives way suddenly or reaches a size sufficient to effect neighboring, physiologically significant, structures by direct pressure. It is this quality of resiliency and the re-

sulting adaptability of the brain tissue which permits the adjustment to the gradually increasing intracranial tension up to the critical point. This explains the delay in appearance and the not infrequent lack of identifying signs and symptoms in a great number of instances of cerebral aneurysms. Suspicion of an aneurysm is aroused most commonly only when its formation is abrupt or when it reaches such a size as to precipitate the symptoms and signs which recently have come to be recognized as those of a probable aneurysm. Still more frequently, this recognition is aided by the sudden development of constellations of clinical manifestations now identified under the term of "spontaneous subarachnoid hemorrhage" (13), a symptom-complex which points to rupture of a cerebral aneurysm.

Thus, the behavior of the common example of an aneurysm reveals itself in a slow and long phase of its development, and a subsequent course which is interrupted at one time or another by an explosive phase, not uncommonly a fatal one. This is an unfortunate situation; the presence of the lesion being unrecognizable until a time when radical therapeutic measures are extremely hazardous or of little value. It calls for efforts in search for leads, which would permit an earlier diagnosis. Some progress has been made so that at present we know that the clinical features of the fully developed cerebral aneurysm in general duplicate those encountered in other expanding intracranial lesions, and as such may be classified as *general* and *focal* in character.

The general symptoms and signs of an intracranial aneurysm: Of these, the most prominent is headache. This is often described as being migrainous in type because of its pulsating character, its abrupt onset and its rapid rise to a high pitch, causing a feeling of giddiness, accompanied by nausea and vomiting, and occasionally associated with visual disturbances. The character of the headaches has led Adie (19) to express the view that serious consideration of a cerebral aneurysm must be given in instances of paroxysmal headache of the so-called ophthalmoplegic migraine.

Convulsive seizures may occasionally usher in a graver phase in the clinical picture.

Tinnitus or a pulsating noise in the head may also be present.

Papilledema, on the other hand, so constant a sign of increased intracranial tension, is a feature often missing in cerebral aneurysms. The same holds true of alteration of pulse and respiration, unless leakage from the aneurysm or vast involvement of cerebral tissue takes place. Naturally, when the appearance of signs of meningeal irritation, the discovery of blood in the cerebrospinal fluid and the presence of retinal hemorrhages, are added to features of increased intracranial tension, there is little doubt as to the existence and the probable state of an intracranial aneurysm.

Focal signs of intracranial aneurysm depend upon their anatomical relationship to essential areas in the brain. Though every large and medium sized vessel is a potential seat of aneurysmal formation, there are,

however, some arterial trunks which are most commonly the seat of these anomalies. The following vessels are usually listed in the order of their greater frequency of involvement: 1) middle cerebral; 2) internal carotid; 3) anterior cerebral; 4) anterior communicating; 5) basilar; 6) posterior communicating; 7) posterior inferior cerebellar; 8) vertebral; 9) ophthalmic; 10) posterior cerebral.

This order of incidence was obtained by combining the statistical data assembled by Fearnside (2), Church (9), Schmidt (17), and Wicher (20). It is rather significant that MacDonald and Korb, analyzing a much larger number of cerebral aneurysms give the same order of frequency with which the cerebral vessels are affected. In our own experience, though based on a small series of cases, there were some striking deviations, which will become obvious as our material is surveyed.

Since some of the vessels at the point of origin of an aneurysm provide the blood supply to related and physiologically significant areas of the brain, there is ample reason for the provocation of manifestations of a localizing character due to direct implications of affected areas by the altered vessels. It is not only the pressure of the aneurysmal distention that causes the local cerebral dysfunction, but also, and maybe more so, the focal retardation or complete arrest of the blood stream.

These circumstances are likely to give rise to substantial diagnostic leads as illustrated by the more common and better known aneurysmal syndromes. This is particularly true of aneurysms of the internal carotid artery where, by the proximity of the expanding vascular sac to the structures running through the cavernous sinus on one hand, and to the optic and olfactory nerves on the other, a group of localizing signs and symptoms are precipitated. They include amblyopia or hemianopias of various types, disc changes in the nature of optic atrophy, loss of sense of smell, paralysis of the homolateral extrinsic and intrinsic eye muscles, exophthalmos, and sensory changes in the distribution of the ophthalmic division of the trigeminal nerve. Should the aneurysm be of considerable size, causing a massive disturbance in the blood supply to a neighboring part of the brain, other focal manifestations may appear, including aphasia, if the lesion is on the left side in a right handed individual.

In instances of aneurysm of the anterior cerebral artery, because of its location in front of the optic chiasm, in the neighborhood of the olfactory nerve and the frontal lobe, visual field disturbances, loss of sense of smell and psychic manifestations may be precipitated. They are, however, not too reliable in definitely locating or identifying the lesion.

With regard to the posterior communicating artery, it is said (and occasionally found) to give rise to oculo-motor palsies and to contralateral pyramidal tract involvement (Weber's syndrome).

The clinical diagnosis of an intracranial aneurysm in the greater number of instances is still a venture too often disappointing in spite of the exist-

ence of such constellations of signs and symptoms, quite characteristic of aneurysms in a few selected locations. This unsatisfactory state of affairs finds its explanation in the already mentioned mood of development and behavior of such a lesion.

In the past, as is still the case, the diagnosis was most commonly established only when a sudden change in the intracranial aneurysm would precipitate a series of events, caused by its rupture or by its massive implication of related brain tissue. In the greater number of such instances a fatal termination ensues and, of these, some come to necropsy thereby disclosing the offending lesion. A definite recognition of the character of the lesion would thus often come too late to influence the management of the case or its clinical course. However, with the increasing availability of non-toxic radiopaque media for diagnostic purposes, substances came to hand which promised to be of decided assistance in the earlier diagnosis of intracranial aneurysm. As recently as 1927, Moniz (21) introduced the use of the *thorotrast* for the visualization of the arterial tree in the brain. This substance was utilized by Dott (22) leading to satisfactory surgical intervention in several cases. Because of the likelihood of it being injurious to the nervous tissue it was abandoned. Recently Gross (23) employed *Diotrast*, another radiopaque medium with good results. Immediately following the injection of this substance into the common carotid artery an x-ray filming of the head is carried out. The vessels at the base of the brain are visualized and any striking alteration in their calibre detected. This substance must be used in proper dilution, quantity and temperature.

Such a method is exceedingly useful in the differential diagnosis and the determination of surgical intervention. However, the greatest advantage from this diagnostic procedure will be obtained only when great care and seasoned judgment are exercised in the choice of subjects best adapted to undergo this procedure.

This caution and demand for a conservative attitude toward this promising diagnostic step, is prompted by the findings in the following case reports, which call attention to the site, size and conditions of the aneurysms as well as to the grave and massive alterations they often cause in the neighboring brain tissue and its coverings.

CASE REPORTS

Case 1. Aneurysm of the anterior communicating artery; two episodes of subarachnoid hemorrhage in the course of thirty years.

History (as given from memory by Dr. B. S. Oppenheimer). "In December 1907 or possibly early January 1908, M. R. M., (G 26), then a man aged 42, became suddenly violently ill: he suffered with excruciating headache and projectile vomiting. When seen by me he already developed neck rigidity and I performed a lumbar puncture. The fluid I obtained was somewhat bloody. The blood was probably not traumatic,

for I was quite expert in doing lumbar punctures at that period as I had been through an epidemic of meningitis at The Mount Sinai Hospital). On a subsequent puncture the fluid was xanthochromic. He was quite sick for over four months, until May of 1908. During that time, I recall, he had headache, paresis of some ocular muscles and absent knee jerks. He was irrational for some time and had involuntary urination and defecation. Dr. Emanuel Libman and Dr. George Jacoby saw him with me in consultation repeatedly. The diagnosis was uncertain: the cerebrospinal fluid was sterile: and the white blood cell count in the fluid was higher than that in the peripheral blood (another reason for believing the blood in the cerebrospinal fluid was nontraumatic). There was no evidence of syphilis either in the history or on examination; and subsequently the Wassermann reaction was found to be negative. He manifested no evidence of nephritis or arteriosclerosis. I recall that I considered serous meningitis, but the slightly bloody fluid did not fit in with that diagnosis. After the first four stormy weeks during which he was irrational, he began to recover gradually. He remained well until the early part of December 1923, when he began to experience precordial (anginal) pain. Two years later, he had an attack of dizziness and vomiting, but this cleared up with rest. He was in constant fear of a recurrence of the 1907 episode. In 1931 an x-ray examination of his chest revealed a widened aorta and the electrocardiogram disclosed a left ventricular preponderance. His blood pressure remained somewhat low until 1932, when it was found to be 154 systolic and 90 diastolic.

"He had always a tendency to spontaneous hemorrhages in his skin, so I referred him to Dr. Alfred F. Hess who failed to throw any light on this condition. These spontaneous hemorrhages appeared not only in various parts of the skin, but on one or two occasions in the subconjunctiva, without known effort such as coughing. In 1933, another electrocardiogram showed left axis deviation, but no positive evidence of myocardial involvement. In 1935 he complained of anginal pains from time to time and his blood pressure was 160 systolic and 104 diastolic.

"On May 27, 1937 he came to my office complaining of periodic headaches for the preceding four months. His sinuses were examined and found not responsible for the headaches. An x-ray examination of the skull was reported as negative. He looked well and his blood pressure was 136 systolic and 80 diastolic. An electrocardiogram showed left ventricular preponderance without evidence of myocardial involvement.

"On July 13, 1937 he returned complaining of pain in the 'appendix region'. His headaches had entirely disappeared. There was no appendicitis.

"He was seen again on September 20, 1937, when he complained of some sacro-iliac pain. He had no symptoms referable to the head.

"On October 30, 1937 he was suddenly seized with "excruciating" headache followed by a rapid development of numbness and weakness of both lower extremities. Very soon thereafter he lapsed into stupor. In view of the bilateral involvement of the lower extremities a diagnosis of sagittal sinus thrombosis was considered. A neurologist was consulted, who found no localizing signs beyond the loss of power in both legs and in view of the history as given to him and the other clinical features he agreed to the probable diagnosis of thrombosis of the superior longitudinal sinus.

"He died within twenty-four hours after the onset of symptoms."

Necropsy findings. Brain. Gross. The brain was voluminous. A large quantity of dark, fluid blood filled the subarachnoid space, particularly in the region of the lateral sulci and along the mesial aspect of the two cerebral hemispheres. A fairly large clot of blood was found in the front of the corpus collosum in the depth of the anterior extension of the dorsal longitudinal fissure. At that point the blood which was found in the subarachnoid space was thickly adherent to the arachnoid and could only be detached with difficulty. At the base of the brain the cisterns were filled with

blood and anterior to the *cisterna peduncularis* and close to the base of the ventral extension of the dorsal longitudinal fissure there was a fairly large, well calcified aneurysm (fig. 1B) springing from the *anterior communicating artery*. It showed a large defect in its middle which was probably the break through which the hemorrhage took place. The other vessels were unusually well preserved and showed a few small atheromatous plaques.

On sectioning the brain, the ventricles were found to be markedly dilated and there was blood within the ventricular system. There was a defect at the base of the brain, creating a communicating channel between the subarachnoid space and both anterior horns of the lateral ventricles (fig. 1A). The tegmentum of the midbrain and pons showed marked disorganization and hemorrhagic extravasation.

Comment. The wall of the aneurysm which was found to be thick and calcified gave evidence of being of old standing. This finding permits the supposition that it pre-existed the first episode of spontaneous subarachnoid hemorrhage. It is, of course, reasonable to assume that the first hemorrhage into the subarachnoid space

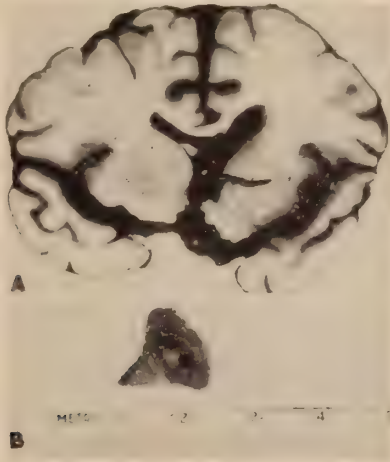


FIG. 1 A (Case 1). Coronal section of the brain, showing ventricular and subarachnoid hemorrhage with the defect at the base of the brain, the seat of the aneurysm.

B. Aneurysm of the anterior communicating artery in Case 1.

was caused by leakage from this aneurysm, as no other aneurysms were found, and the condition of the one found could well account for the first hemorrhage. It is a rather striking history but, nevertheless, points definitely to the possibility of a patient recovering from a ruptured aneurysm and remaining undisturbed by the aneurysmal vessel for thirty years, until the vessel, undergoing progressive degenerative changes, suffers a larger break to cause a fatal hemorrhage into the subarachnoid space and through a defect in the brain the flooding of the ventricular system. Of interest also are the hemorrhagic skin and conjunctival lesions, manifestations not uncommonly encountered in instances of cerebral aneurysms.

Case 2. Aneurysm of anterior communicating artery, with terminal intracerebral, intraventricular and subarachnoid hemorrhage.

History (Adm. 547499; P.M. 10962). E. S., a woman, aged 50 years, entered the hospital on October 28, 1938. At the age of 12 she had passed through an episode

of urinary retention lasting six days, following which she said she was afflicted by a "crippled spine." During the year before her admission to the hospital the patient had had several conjunctival hemorrhages in the left eye, each of which lasted a few weeks. She had also experienced occasional headaches. Two nights before her admission she suddenly awoke and discovered that her middle and ring fingers of the right hand felt swollen and numb. These sensations lasted about five minutes. On the morning of her admission to the hospital she was on her knees washing the floor and, while attempting to rise, was seized with a sudden severe headache and fainted. She regained consciousness in a little more than one hour, (according to her husband) and complained of occipital headache.

Examination. The patient was moderately cyanotic and her conjunctivae were very pale. She vomited shortly after her admission; and seemed to have pain in the head, but fell asleep when left undisturbed. The heart sounds were distant and of poor quality. The blood pressure was 120 systolic and 80 diastolic.

Neurological status. The pupils were unequal, the right larger than the left and the optic discs showed moderate temporal pallor; there were two flame shaped hemorrhages in the right fundus. The deep reflexes were hyperactive. Only the left upper abdominal reflex was elicited. The plantar response was equivocal on both sides. There was some impairment of recent memory.

Laboratory data. Urine: albumin, one plus. Cerebrospinal fluid: bloody; initial pressure, 240 mm. of water; Ayala index, 2.3. Blood count: 17,000 leucocytes with 90 per cent polymorphonuclear neutrophils. Hemoglobin, 70 per cent. Blood Wassermann test, negative. Blood sugar, 125 mg. per cent; urea nitrogen, 23 mg. per cent.

Course. The diagnosis of an intracranial hemorrhage, either intracerebral or subarachnoid, with bleeding into a tumor as another possibility, were considered. On the second day in the hospital stiffness of the neck developed. A slight weakness of the right side of the face appeared. The Hoffman sign appeared on both sides; and the Babinski sign became frankly positive on the left side. On the third day her headache had subsided and all abdominal reflexes became active. The rigidity of the neck subsided and the Babinski sign disappeared. She complained of a sensation of pressure within her eyeballs, which were found tender to pressure. Toward evening of that day she suddenly developed Cheyne-Stokes breathing for a period of five minutes, and a marked generalized pallor, remaining, however, fully conscious. Her pupils were noted to be small though equal and active. On the fourth day she complained of general weakness and headache. At this time the right pupil was found to be larger than the left. On the fifth day fresh hemorrhages were noted in both fundi. On the eighth day she displayed mental signs, was noisy, alternately facetious and irritable. On the ninth day she passed through a convulsive episode when she was found staring into the distance and apparently unconscious. The upper limbs were in flexion, the lower limbs being extended. Several minutes later her head turned to the left and clonic movements of the left arm and leg set in. There was noted bilateral ptosis of the eyelids, especially of the right, and respiration became stertorous and irregular. She sank into coma. A lumbar puncture yielded bloody cerebrospinal fluid under increased pressure (450 mm. of water). She died shortly afterwards.

Necropsy findings. Brain. Gross. Over both temporal lobes there was diffusely spread dark and clotted blood. Reddish discolorations were scattered over both convexities. The right Sylvian fissure contained a blood clot. An extensive dark subarachnoid blood clot obscured the base of the brain, and was also present over the cerebellum. Blood filled the cerebello-medullary cistern and encircled the spinal cord in its cervical segments.

The junction of the middle cerebral arteries with their corresponding posterior

commissural arteries looked grossly normal. The right olfactory sulcus was damaged during the removal of the brain and on inspection this region presented a projecting blood clot.

On sectioning of the brain, a hemorrhage within the left frontal pole was found extending backwards to involve the corpus callosum (fig. 2A). At that point the hemorrhagic mass was continuous with one in the adjacent anterior horn of the lateral ventricle. Both lateral ventricles, the third ventricle, the aqueduct of Sylvius, and the fourth ventricle were all filled with blood. A ruptured aneurysm was found attached at a point of junction of the two anterior cerebral arteries (fig. 2B). It seemed to gravitate to the left.

Comment. Apparently the course of events in this instance was as follows: The aneurysm caused the formation of an area of encephalomalacia in the left frontal lobe. This, as the aneurysm ruptured, served as an area of lowered resistance and permitted the bleeding to spread into the area of softening. The blood ultimately

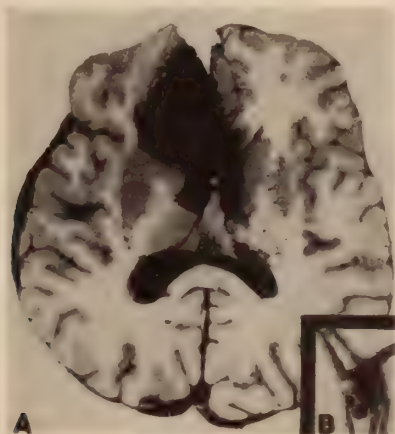


FIG. 2 A (Case 2). Longitudinal section of the brain, showing intracerebral, intraventricular and subarachnoid hemorrhage. Note defect in anterior horn of the lateral ventricle.

B. Aneurysm of the anterior communicating artery in Case 2.

broke through a zone of necrotic tissue into the adjacent ventricular compartment, this in turn was followed by the spread of the blood through the subarachnoid space.

Of significance are some of the events in the past history of the patient. The vague cerebral manifestation in her childhood, such as the urinary retention and "crippled spine," could well have been a mild leakage from a congenital aneurysm, the same aneurysm which at the age of 50, 38 years later caused the fatal bleeding. The conjunctival hemorrhages, which appeared during her last year of life, is a condition often encountered in instances of cerebral aneurysm. It was found also in Case 1.

Case 3. Aneurysm of anterior communicating artery.

History (Adm. 477618; P.M. 11944). L. H., a man, aged 56, was admitted to the hospital with a temperature of 102°F. and too acutely ill to give a detailed history. He was in the habit of consuming more than one pint of alcohol a day for many years until six years ago when the onset of severe headaches forced him to stop drinking. These headaches would recur several times a month, would last several

hours and disappear spontaneously. Six days before entering the hospital, while reading, he felt his head and face suddenly suffuse with blood; simultaneously he developed an intense occipital and frontal headache which persisted day and night to the time of admission, preventing sleep and work.

Examination. Temperature 101.2°F. Pulse 88. Respiration 20. The patient was a thin middle aged man, apparently in distress from constant frontal headache. His face was so flushed as to suggest a "sunburn." His blood pressure was 135 systolic and 70 diastolic. His sensorium was clear. There was slight eyeball tenderness. There was neck rigidity accompanied by a bilateral Kernig sign and unequal pupils, the right being larger than the left. Hypertensive retinopathy was noted. Meningeal irritation due to subarachnoid bleeding was diagnosed.

Laboratory data. Urine, blood chemistry and serology, hemoglobin and red blood cell count were within normal limits. White blood cells, 12,000 per cu. mm. with a normal differential count. A lumbar puncture disclosed grossly bloody cerebrospinal fluid with successive specimens being identical. The initial pressure of 170 mm. of water dropped to 90 mm. of water with removal of 20 cc. of fluid. The supernatant fluid was xanthochromic. Electroencephalographic studies showed a "slight degree of diffuse cerebral dysfunction. No indication of focal pathology." An electrocardiogram was reported as negative.

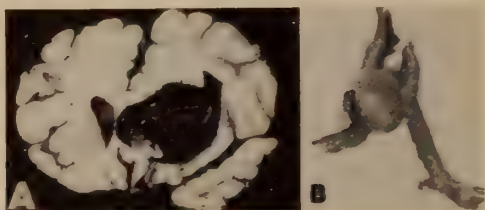


FIG. 3 A (Case 3). Coronal sections of the brain, showing the large defect in the frontal lobe communicating with the homolateral ventricle.

B. Aneurysm of the anterior communicating artery in Case 3.

Course. His condition remained satisfactory except for a daily rise in temperature, ranging between 99° and 102°F. A second lumbar puncture on the fourth day showed the initial pressure to be 160 mm. of water; cerebrospinal fluid was yellow and gave a four plus Pandy reaction; there were no red blood cells. On the seventh day the patient suddenly began to breathe stertorously and failed to respond; 10 minutes later his left eye remained open while the right was closed and both pupils were dilated and failed to react to light. The deep reflexes were exaggerated and there was a bilateral Babinski sign. The neck was rigid and the Kernig signs were marked. Another lumbar puncture showed grossly bloody cerebrospinal fluid with an initial pressure of 400 mm. of water. The patient developed convulsive movements of his head and left hand and died an hour later.

Necropsy findings. Brain. Gross. A large area of softening was present in the right frontal pole; it was occupied by a blood clot measuring 5 cm. in diameter and projecting into the subarachnoid space through a 1 cm. opening on the antero-inferior surface of the right frontal lobe (fig. 3A). During manipulations, the clot was accidentally expressed from the cavity. The blood vessels at the base of the brain showed moderate arteriosclerotic changes and the circle of Willis, though intact, appeared compressed and distorted by the right cerebral pathology. An aneurysm of the right anterior cerebral artery was found. A second, smaller focus of softening was discovered on the postero-inferior surface of the left cerebellar hemisphere.

Small blood clots were present in the cisterna magna and basalis. On further investigation a small circular aneurysm (fig. 3B) was found arising from the anterior communicating artery. A small opening was noted in that aneurysm but it was difficult to say whether it was not artificially produced for it was not surrounded by extravasated blood.

On sectioning a large area of hemorrhage was found extending from the tip of the frontal lobe all the way back through the white substance reaching a point on a level with the posterior end of the corpus striatum. This hemorrhage was found in the right hemisphere and occupied almost the entire white substance in the anterior two-thirds of the frontal lobe. Posteriorly it extended so as to almost completely destroy the white matter of the insula laterally without impinging upon the striatum and the internal capsule. A small hemorrhagic area was found in the midbrain in its right tegmentum. Coagulated blood was also found in the lateral ventricle on the side homolateral with the hemorrhage. Blood was also found in the fourth ventricle and some in the third ventricle. On removal of the blood clot a cavity showed a discolored wall and on sectioning, there was an impression of a thin capsule lining the cavity.

Case 4. Aneurysm of right anterior cerebral artery, with recurrent episodes of spontaneous subarachnoid hemorrhage; clinical picture of sinus infection.

History (Adm. 413991; P. M. 10515). I. P., a young man, an instructor in physical training, 31 years of age, was brought to the hospital for the first time on August 20, 1937. Two months previously, he passed through an episode of sudden chilliness and generalized weakness. The next day while bending over he was seized with sudden and severe pain at the back of his head. This pain persisted for several days. He was seen by a physician who treated him successfully for sinusitis and his headaches soon disappeared. He remained well for about six weeks. On August 2, while performing calisthenics, the headache suddenly returned and was accompanied by stiffness of the neck and a feeling of faintness. No account was available of his condition during the next 11 days, but at the end of that period, severe headaches set in and on August 13, while exercising, he suddenly lost consciousness for a few minutes. With the return of consciousness, he experienced severe pain in the front and on top of his head. He was again treated for sinusitis, and at first seemed to improve, but on the day before admission severe headache and stiffness of the neck returned and persisted.

Examination. The patient appeared acutely ill; he was somewhat drowsy. There was slight tenderness over the frontal and ethmoid sinuses and a profuse mucopurulent postnasal discharge was present. His head was held in slight retraction, the neck was stiff and a bilateral Kernig sign was elicited. The blood pressure was 118 systolic and 72 diastolic.

Laboratory data. The cerebrospinal fluid was xanthochromic and contained 8700 red blood cells and 650 white blood cells per cu. mm. of which 64 per cent were polymorphonuclear leucocytes; its initial pressure was 140 mm. of water. There were no organisms on smear; a culture of the fluid was negative; sugar 15 mg. per cent; chlorides as sodium chloride, 640 mg. per cent; total protein 108 mg. per cent. Blood: white blood cells, 17,200 per cu. mm., of which 74 per cent were polymorphonuclear leucocytes. Other blood examinations, including the Wassermann test were negative as was the urinalysis. X-ray examination of the sinuses and of the spine were reported as negative.

Course. Mucopurulent material was obtained on irrigation of the ethmoid sinuses. Because of the high proportion of leucocytes in the cerebrospinal fluid, it was felt that the sinusitis was an important factor in producing the meningeal irri-

tation. A bilateral sphenoethmoidectomy was performed and an empyema of the right sphenoid was found as well as a left sphenoiditis, and bilateral ethmoiditis. A culture of the pus showed *B. coli* and *Staphylococcus albus*. A biopsy of the mucous membrane was reported as showing no significant changes.

During the patient's nineteen days in the hospital the stiffness of the neck and the headache gradually diminished and he was symptom-free as he left the hospital. His first four days at home were spent in bed while apparently maintaining good progress toward recovery, but on the morning of the fifth day he was awakened by headache and five minutes later passed through a convulsive episode. He was brought to the hospital two hours later.

Examination (second admission, September 13, 1937). The patient was confused and incoherent. His blood pressure was 90 systolic and 60 diastolic. The pulse rate, 55 per minute; the temperature, 96.4°F.; and respirations 16 per minute. He displayed stiffness of the neck and a bilateral Kernig sign. Both discs were slightly blurred. The pupils were small (he received morphine shortly before admission). All the deep tendon reflexes were considerably depressed. There was no response

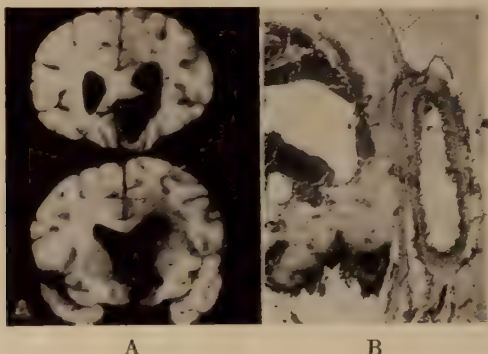


FIG. 4 A (Case 4). Coronal sections of the brain showing a large hemorrhagic defect in the frontal lobe, communicating with the homolateral ventricle.

B. Section showing recanalization of partially thrombosed aneurysm in Case 4.

to plantar stimulation. The cerebrospinal fluid was found to be bloody with an initial pressure of 340 mm. of water.

Course. Three hours after admission, the patient became comatose. There appeared an occasional convulsive movement of the upper eyelids. The pulse and respirations gradually slowed and he ceased five and one-half hours after admission.

Necropsy findings. Brain. Gross: There was a mass of clotted blood covering the midbrain, pons and medulla and totally obscuring the structures at the base of the brain.

On sectioning, the first striking alteration that came into view was the presence of a circumscribed area of softening into which the hemorrhage took place. This area was found directly underneath the genu of the corpus collosum, very close to the lip of the anterior ventral extension of the dorsal longitudinal fissure (fig. 4A). It occupied almost the entire vertical axis of that part of the brain and extended laterally for about 1 cm. On tracing this area backward; it was found to become continuous with a defect in the floor of the anterior horn of the lateral ventricle on the right side. From that point on the blood clot could be traced into the entire ventricular system, which was markedly enlarged and somewhat symmetrical except for the dislodged and deformed ipsilateral anterior horn. A search for the probable origin of the hemorrhage revealed an area of granulation tissue in the

region of the anterior commissure and within the ventral extension of the dorsal longitudinal fissure. It outlined the right anterior cerebral artery, and was very likely the seat of an aneurysmal defect through which the hemorrhage took place. Histological studies verified this assumption (fig. 4B). The aneurysm was found to be partially thrombosed and recanalized. The exposed vessels at the base of the brain showed isolated atheromatous patches.

Comment. We doubt whether any extenuating circumstances can be advanced in defense of the failure to diagnose the case during the earlier clinical course. It is true that the presence of a relatively high white blood count in the cerebrospinal fluid was a misleading finding, but it is not an unusual finding and when occurring in fluid frankly xanthochromic and sterile, it should not lead one astray from the diagnosis of spontaneous subarachnoid hemorrhage. A similar error of diagnosis under very similar conditions was made in another instance (Case 9 in this series). Of course, a sudden onset of symptoms with loss of consciousness accompanied by a rise in temperature, and the development of meningeal signs, when added to the xanthochromic cerebrospinal fluid should have left no doubt as to true diagnosis.

Case 5. Multiple aneurysms in the course of branches of the right anterior cerebral artery, long clinical course punctuated by attacks of Jacksonian epilepsy.

History (Adm. 243440; P.M. X314). I. S., a woman, aged 59, had had seven children. The patient and most of her children were subject to recurrent nose bleeds. At the age of 27, for a period of two years, the patient had a few infrequent "epileptic" attacks. At that time and following a pregnancy she was said to have had some "kidney trouble," accompanied by acute symptoms, bloody urine, swollen feet and a period of unconsciousness. For a period of 28 years she remained free from seizures until about two years prior to her admission to the hospital, when convulsive attacks returned and recurred about once every three or four months. During the two months before admission these so-called epileptic attacks became more frequent, recurring from one to four times a week. These convulsive seizures had a sudden onset, with the patient falling to the ground, her body becoming rigid, the eyes glassy, and the face cyanotic with froth appearing at the mouth. The attack would last for about twenty minutes, and was followed by a dazed state and the development of severe pain in the back of the head. For the twenty-four hours preceding her entry to the hospital, the attacks had become still more frequent, occurring at half hour intervals, with the patient remaining in a stupor between attacks from which she could be roused only with difficulty.

Examination. The patient was in coma; there was no uremic odor. The pupils were unequal, the left dilated and fixed, the right contracted and reacting very sluggishly. Convulsive attacks occurred every half hour. The twitchings would begin on the left side of the face and spread to the arm and leg of the same side and then to the right side. The contractions were clonic in character, and more marked on the left side than on the right. A lumbar puncture yielded clear cerebrospinal fluid under increased pressure, containing a few red blood cells. The blood pressure was 140 systolic and 77 diastolic. There was apparently no loss of motor power; all the deep reflexes were very active, more so on the left side; the abdominal reflexes were absent. The left optic disc had a clear margin and marked pallor; the vessels were thin walled and not tortuous.

Laboratory data. Blood Wassermann reaction, negative. Blood chemistry: Urea nitrogen, 23.1 mg. per cent; non-coagulable nitrogen, 51 mg. per cent; uric acid, 31 mg. per cent; creatinin, 1.1 mg. per cent.

Course. The diagnosis made at this time was essential epilepsy and status epilepticus. Large doses of chloral (hydrate) and phenobarbital were administered with some beneficial results for the first two days. The patient became more alert and cooperated somewhat better. However, a definite left hemiparesis was then noted and a left Babinski sign was now elicited. The left pupil was large and fixed to light. Convulsions still occurred, though less frequently, but were of longer duration; they were more marked on the left side. At this time encephalitis or multiple (metastatic) neoplasms were considered in the diagnosis. The patient's improvement was short lived and her condition soon began to decline. The convulsive seizures had again become more frequent. They were preceded by vertigo and would begin in the left side of the face. The mouth was drawn to the left, the eyes turned to the left, the left eyelids would close, the left arm would flex slowly, and simultaneously the left leg would begin to flex. Consciousness apparently was not lost for the patient would remember questions asked during the attack. Directly after an attack, the left hemiparesis would become more marked. The fre-



FIG. 5 (Case 5). Coronal sections of the hemisphere showing the marked calcification of one and the large size of another aneurysm.

quency of such attacks, their Jacksonian character and the fairly satisfactory localizing signs pointed to a right frontal lobe lesion. An x-ray examination showed marked dilatation of the right anterior diploic veins merging into a calcareous mass lying in front of the motor area. This suggested a meningeal tumor and an exploratory craniotomy was thought advisable. This was done and several tumor masses were found on the surface of the cortex, each globular in appearance and enveloped by a thick capsule; another small mass could be felt in the depth of the brain substance. No attempt at their removal was made. The patient died twenty-four hours after the operation.

Necropsy findings. Brain. Gross. The right frontal lobe was small, the gyri were atrophic and thrown into supernumerary folds. On the surface of the brain near the dorsal border, there was a large vessel growing forward and parallel to the dorsal border and terminating in a small sac about 1 cm. in diameter (fig. 5). The sac was embedded in a depression about 5 cm. posterior to the frontal pole. On elevating the sac a depression was found, lined by smooth and glistening pia. Directly posterior to the sac there was another elevation measuring on the free surface about 1.5 cm. in diameter. On cutting into the brain at this point, another

larger, encapsulated mass was revealed. This was oval in outline, measured 3 cm. in the long diameter and was embedded deeply in the substance of the frontal lobe. A cut section of this mass showed it to be hard, somewhat brittle, grayish-brown, and giving the impression of an organized thrombus in an aneurysmal cyst. Directly posterior to this, extending back as far as the upper termination of the post-central gyrus, there were several similar cysts varying in size from 0.5 to 2 cm. in diameter. The smaller cysts were also well encapsulated, surrounded by thick, fibrous, calcified walls. Their cavities were filled with yellowish, granular material and a small amount of yellowish fluid; the inner lining of the walls, however, was smooth, grayish-white and glistening. All the cysts were easily dislodged from the substance of the brain, leaving behind smooth surfaces of only moderately softened brain substance. The vessels at the base of the brain displayed fairly marked arteriosclerotic changes.

Microscopic anatomy. Cross section through the aneurysmal sacs and adjacent cerebral cortex showed that the wall of the sacs had retained some of the histological features of a medium-sized vessel wall with its division into adventitia, media and a markedly distorted intima. The last was fused with a highly organized thrombus which had undergone canalization. The nerve tissue adjacent to the aneurysms showed evidence of softening, and mild infiltrative changes with small round cells, apparently a reactive change.

Comment. This case is an uncommon example of multiple aneurysms, provoking signs and symptoms of an intracranial neoplasm. It is quite reasonable to assume that the early epileptic seizures were due to the formation of the aneurysmal dilatation of the vessels. But as the resilience of the brain permitted its adjustment to the presence of these slowly expanding lesions, the epileptic seizures came to a stop. As the patient became older and degenerative changes took place in the blood vessels, particularly in their aneurysmal expansions and the brain substance lost some of its adaptability, the aneurysms began again to act as irritative foci, with the consequent recurrence of epileptic attacks. It is quite possible that the balance of the equilibrium in the normal brain function was disturbed not only by the presence of the aneurysms but also by the degenerative changes concomitant with the advancing age.

Case 6. Aneurysm of the left middle cerebral artery, close to point of origin from the internal carotid. Recurrent episode of spontaneous subarachnoid bleeding.

History (Adm. 405184; P.M. 10263). J. V., a 37 year old shoemaker, entered the hospital for the fourth time. His first admission took place in the spring of 1935 when he displayed signs of spontaneous subarachnoid hemorrhage. On the second admission a left inferior nasal quadrant defect in the visual field was present. This was already noted during his first stay in the hospital, and led to the suggestion by one member of the staff (Dr. Globus) that it was due to a congenital aneurysm involving the left anterior cerebral artery. On his third admission, (September 1, 1936) he entered the hospital mainly for a lumbar puncture, which revealed the following: 3,500 crenated red blood cells per cu. mm.; the supernatant fluid was clear and colorless; the Pandy reaction was positive. In the intervals between these admissions, the patient was repeatedly examined in the follow-up clinic, where he reported that he was at work and free of complaints. His fourth admission was prompted by the onset of severe headaches. At this time he showed a complete loss of vision in the left eye, pallor of the left nerve head, and a questionable left facial weakness. The blood pressure was 120 systolic and 84 diastolic.

Course. A lumbar puncture at this time yielded xanthochromic fluid. Ten minutes after the tap the patient vomited and lapsed into stupor, his breathing becoming Cheyne-Stokes in character. The left pupil was noted to be larger than the right; both did not react to light. There were, however, no signs of meningeal irritation. The patient rapidly declined and death took place four hours after admission.

Necropsy findings. Brain. Gross. At the base of the frontal lobe the left olfactory tract was displaced laterally by a mass which was imbedded in the left frontal lobe

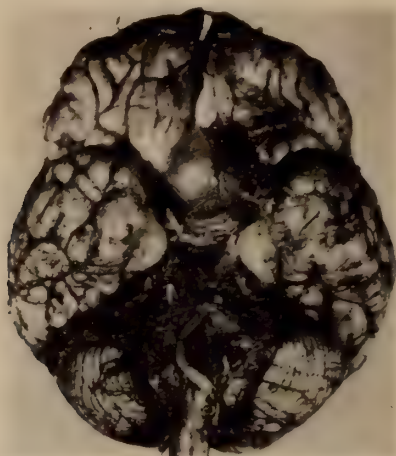


FIG. 6 (Case 6). The base of the brain showing size and location of aneurysm.

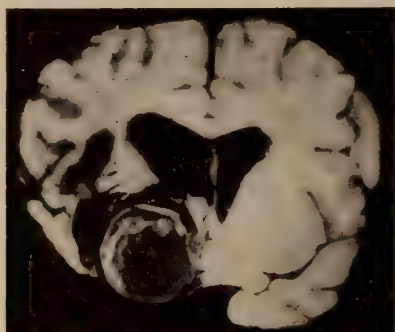


FIG. 7 (Case 6). Coronal section of brain showing location of aneurysm and its disorganizing effect on adjacent brain tissue. Note the communication of the defect with the homolateral ventricle.

immediately adjacent to the midline (fig. 6). Further posteriorly was a great deal of free blood in the interpeduncular space and the basal cisterns. In the left frontal lobe there was a mass which measured 2.5 cm. antero-posteriorly and laterally. This mass was harder to palpation than the surrounding cerebral tissue. It was situated at the origin of the left anterior and middle cerebral arteries. This mass also displaced the left olfactory nerve laterally and compressed the left optic nerve. Posterior to the optic chiasm in the interpeduncular space and covering the ventral surface of the pons and medulla and extending into the cisterna magna was a con-

siderable amount of hemorrhage. The vessels at the base of the brain revealed no atheromatous alterations.

On sectioning the brain, the aneurysm (fig. 7) was found to be lodged in the depression of the left hemisphere on the orbital surface. This depression measured across about 3 cm. and in a vertical plane about 2 cm. Part of the wall of this excavation or depression was made up of a layer of necrotic tissue forming the floor and part of the lateral wall of the anterior horn of the left lateral ventricle. Passing backward on this level there was seen a small hemorrhagic area occupying the space directly outside of the corpus striatum. When this area was traced backward it was found to enlarge and be occupied by a large massive hemorrhage.

Comment. In order to find the source of the hemorrhage into the brain substance, the aneurysm was dislodged and found to be attached at one point in its anterior-most extremity to granulation tissue. On dissecting this granulation tissue, an opening was found in the aneurysm. This opening was not thought to be the one which caused the hemorrhage, but there was every evidence to indicate that contiguous to this defect there was a smaller one now buried in the granulation tissue which was responsible for the bleeding. It is also very likely that at this point the structure of the tissue was defective. Its necrotic tissue separated it from the anterior horn and gave one the impression that it was through this defect that the blood found its way into the ventricular system. This defect communicated with the cavity into which the aneurysm fitted. The aneurysmal cavity was also filled with blood and in turn, communicated with the area of massive hemorrhage. There was another defect communicating the lateral ventricle with the area of hemorrhage and that was in the temporal lobe. So it is probable that the blood found its way into the ventricular system through more than one defect. The ventricles were enlarged and filled with blood. The left ventricle was greater than the right, in spite of the fact that it was adjacent to the aneurysm. This would indicate that it was very likely filled with blood earlier than the ventricle and because it was filled with blood first, it was larger. The four recurrences of bleeding from the aneurysm need not be discussed at length here, for this is more commonplace than exceptional. The areas of brain disintegration resulting from the aneurysm and leading to intracerebral and intraventricular hemorrhage need also not be regarded as a rarity, only as a less commonly realized condition.

Case 7. Aneurysm of the internal (right) carotid artery.

History (Adm. 480245; P.M. 12003). R. P., a woman, aged 53, entered the hospital on October 10, 1941. She was apparently well until four weeks previously when, having ridden in an automobile for five hours, she suddenly began to vomit and shortly thereafter fainted. She remained unconscious for about one hour. She was taken to a hospital where she was given glucose intravenously. She remained in the hospital for six hours and was then brought to New York by train. She was quiet, but complained of slight occipital headache and low back pain. During the next two days she remained at home complaining of slight nausea, increasing headache and low back pain. The latter radiated laterally and was aggravated by movement of the leg. Eight days before entering the hospital she again began to vomit; with this she developed a shaking chill lasting a few minutes and then fainted. This time she was unconscious for about a half hour. On regaining consciousness, she again complained of low back pain, headache, and for the first time of stiffness of the neck. On the day before entering the hospital her temperature was elevated, she had urinary retention and was constipated. She complained of headache. In the middle of the night she became psychotic and overactive, disoriented and would scream if anyone would touch her neck.

Examination. The patient appeared to be acutely ill, dehydrated and uncoöperative. Her blood pressure was 138 systolic and 88 diastolic. The neurological status disclosed the following: She was drowsy, confused, disoriented, and displayed a tendency to confabulate. There was bilateral blurring of the nasal margins of the discs and there were several hemorrhages in the left disc. The pupils were unequal, the right greater than the left. They reacted to light. There was a left hemiparesis, most marked in the leg. The deep reflexes on the left side were diminished. The left ankle jerk and the left abdominals were absent. A Babinski sign was present on the left. There was marked stiffness of the neck with bilateral Kernig sign.

Laboratory data. The cerebrospinal fluid was xanthochromic at first and then became grossly bloody. The initial pressure was 180 mm. of water. The cerebrospinal fluid Wassermann and colloidal gold tests were negative. The urine was negative. The blood showed a moderate leucocytosis.

Course. The clinical impression was that there was an aneurysm of the right internal carotid at its junction with the anterior cerebral artery. The temperature for the first four hospital days was 102°F., pulse and respirations were normal. By the fifth day, however, the temperature had returned to normal and there was no subsequent rise during her hospital stay. The patient's headache and mental confusion were somewhat improved, but she continued to be drowsy and her speech was slow and hesitant. Nuchal rigidity persisted as did the left hemiparesis. A lumbar puncture done two weeks after admission disclosed clear xanthochromic fluid under an initial pressure of 80 mm. of water; microscopic examination showed 16 lymphocytes per cubic millimeter. Gradually, the paresis of the left upper extremity improved but the left crural monoplegia persisted. A lumbar puncture performed three weeks after admission disclosed xanthochromic fluid containing 9,250 red blood cells per cubic millimeter. The day following this puncture, the patient's drowsiness increased, her respirations became irregular and there occurred an episode in which she stiffly extended both arms and then lapsed into stupor. At that time, her pupils were first small and reacted to light, but shortly thereafter they became dilated and fixed to light. There was marked stiffness of the neck and no response to painful stimuli. The deep reflexes were active in the upper extremities, more so on the left; they were active in the left lower extremity, but depressed on the right. There was a bilateral Babinski sign. A lumbar puncture showed grossly bloody cerebrospinal fluid under an initial pressure of 70 mm. of water. A few hours later the patient ceased.

Necropsy findings. Brain. Gross. The brain was under increased pressure. It showed a diffuse congestion of the vessels. At the base of the brain in the vicinity of the right gyrus rectus there was a projecting reddish mass. In its length it extended from the temporal pole to the optic chiasm. In its width it occupied the entire gyrus rectus. It projected about a half centimeter beyond the surface of the cortex. When dislodged it left behind a large cavity with a smooth lining. At the posterior end of this cavity there was a large aneurysm projecting from the direction of the internal carotid and the anterior cerebral artery on the right side. It apparently contained a large thrombus and was surrounded by a fairly thick layer of granulation tissue. The interpeduncular space seemed to be filled with coagulated blood and granulation tissue. The cisterna pontis and cisterna magna were filled with blood. The vessels at the base of the brain were moderately sclerotic.

On sectioning of the brain, a large area of softening was found in the frontal lobe occupying its ventral portion (fig. 8). This cavity was irregular in outline and measured 4 cm. in its width and 7 cm. in its length. It extended from the frontal pole as far back as the point on the level with the foramen of Monro. The cavity was filled with coagulated blood. Its lining was brownish in color and showed trabeculations and spots of softening. Most of the lining was rather smooth and its discoloration

penetrated for a distance of about 2 mm. Another area of softening was found directly below the capsule on the right side. It was elongated and followed the course of a large branch of the middle cerebral artery. This cavity can be traced as far back as about the middle of the insula. On the level of the optic chiasm there was a large aneurysm measuring about 1.5 cm. in its longest diameter. It corresponded in location and outline to the internal carotid artery at the point where it gave rise to the middle cerebral artery. Further anteriorly it probably was continuous with the anterior cerebral artery. The lateral ventricles were dilated and filled with blood, but not displaced. The rest of the ventricular system was also filled with recently clotted blood.

Comment. The course of events in this instance was as follows: An aneurysm of old standing arising from the internal carotid artery at the point of its junction

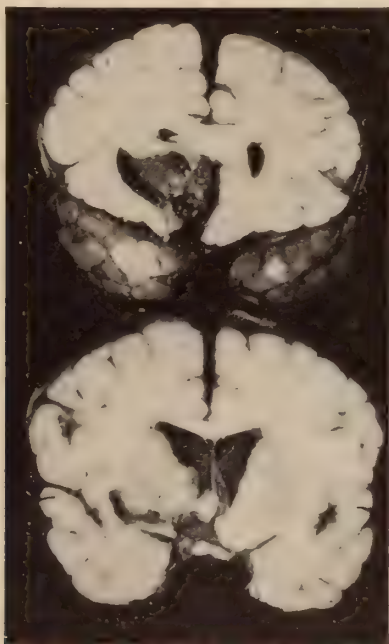


FIG. 8 (Case 7). Coronal sections of the brain showing the hemorrhagic area in the right frontal lobe, its communication with the ventricular system, and the aneurysm which is thrombosed and imbedded in the disorganized brain tissue at the base. See lower illustration.

with the middle cerebral artery produced softening particularly in the frontal lobe in the region of the blood supply derived from the anterior cerebral artery. In time further disintegration of the aneurysm led to bleeding and this bleeding found its way first into the area of softening and later through a defect in the zone of softening into the ventricular system thereby causing the fatal termination.

Case 8. Aneurysm of posterior communicating artery; displaying residual granulation tissue at point of previous spontaneous subarachnoid bleeding.

History (Adm. 309542; P.M. 7034). A. D., aged 36 years. Seven years before her admission to the hospital, while under the stress of a violent emotional outburst,

she developed intense pain in the left frontal region with restlessness and insomnia. Two months later she suddenly experienced transient double vision and pain over the left eye. Two weeks prior to admission, the pain in the left frontal region suddenly returned, and she became stiff "all over" and exceedingly weak. The headache now became generalized and the pain spread down the spine and along the left forearm. This was accompanied by elevation of temperature and an occasional chilly sensation.

Clinical findings and course. The left pupil was dilated and fixed to light. There were marked rigidity of the neck, a bilateral Kernig sign, depressed deep reflexes, and slight weakness and tremor of the left hand. A lumbar puncture yielded uniformly bloody cerebrospinal fluid which showed xanthochromia on standing. The blood pressure was 142 systolic and 90 diastolic. The Wassermann tests of the blood and cerebrospinal fluid were negative. The urine contained only a trace of albumin. The blood count showed white blood cells, 11,400; polymorphonuclear leucocytes, 66 per cent. The patient did not convalesce satisfactorily and on the twenty-third day in the hospital she suddenly passed into stupor. The pulse became unusually



FIG. 9 (Case 8). Aneurysm of the posterior communicating artery, in a state of advanced disorganization imbedded in necrotic brain tissue.

slow and a lumbar puncture at that time revealed bloody cerebrospinal fluid. She died several hours later.

Necropsy findings. Brain. Gross. The meninges were dull and showed patchy discoloration, particularly of the left frontoparietal region, where there was a large amount of blood in the subarachnoid space. In an attempt to dissect structures in the interpeduncular space, old adhesions were found, especially on the left side, making it difficult to separate the left branches of the circle of Willis. The left posterior communicating artery was surrounded by dense granulation tissue and was adherent to the adjacent inferior surface of the left temporal lobe (fig. 9). In the course of dissection a small sac broke off from the somewhat thickened posterior communicating artery. The inferior surface of the left temporal lobe showed marked softening and through a small opening, most likely artificially produced, blood escaped on the slightest pressure on that lobe. The ventricles were greatly distended with blood. A section of the vessel close to the aneurysm displayed advanced disorganization of its structure. The vessels at the base of the brain showed moderate arteriosclerotic changes.

Comment. In this case the aneurysm which ruptured and caused the fatal issue certainly existed for a period of years, as the history of headache and diplopia would indicate. The adhesions found in the region acted as a protective coat for the degenerated wall of the aneurysm and held off the terminal hemorrhage. The blood in the ventricles resulted from the extravasation which took place through an erosion caused by the aneurysm in the adjacent brain substance.

Case 9. Aneurysm of posterior cerebral artery, simulating a posterior fossa neoplasm.

History (Adm. 128124; P.M. 5839). L. B. a woman, aged 30, who was admitted to the hospital for the first time on April 3, 1927, had had intermittent headaches for about two years. For six months prior to admission the headaches had become more severe and were localized in the frontal region. One week before admission there developed severe pain in the back and stiffness of the neck. She vomited several times, and had several generalized convulsions, lasting from two to three minutes. On the day preceding admission, there was a slight elevation of temperature.

Examination. There was rigidity of the neck; a bilateral Kernig sign; bilateral papilledema, and generalized hyporeflexia; the abdominal reflexes, except for the upper left, were absent.

Course. A lumbar puncture yielded xanthochromic cerebrospinal fluid; the initial pressure was 340 mm. of water; there were 33 lymphocytes per cubic millimeter. The following day another lumbar puncture was performed and the cerebrospinal fluid was again found to be xanthochromic. A blood count showed: white cells 12,000, with 58 per cent polymorphonuclear leucocytes. The Wassermann reaction of the cerebrospinal fluid was negative. The blood pressure was 110 systolic and 68 diastolic. On the third day in the hospital, a vertical nystagmus was noted. Six days later, an encephalography was performed; it disclosed moderately dilated lateral ventricles, while the third ventricle was poorly outlined. In the antero-posterior view, the ventricular system was apparently displaced to the left, and the right anterior horn seemed to be somewhat larger than the left. Coloric tests showed no involvement of the semicircular apparatus. A diagnosis of neoplasm of the posterior fossa was, nevertheless, made. On the sixteenth day in the hospital, a suboccipital craniotomy was performed; but no tumor was found. The patient showed some subjective improvement and left the hospital forty-six days after admission. Throughout her stay in the hospital her temperature varied between 98° and 102°F.; the pulse rate varied between 80 and 96.

Second admission. The patient was re-admitted one month later, on June 27, complaining of more severe and constant headaches. Her pupils were irregular; and there was bilateral papilledema, though not as marked as previously. There was now a right facial weakness, and her tongue deviated to the right. Twelve days after the second admission, a ventriculography was performed; 60 cc. of clear cerebrospinal fluid was withdrawn and replaced by air. Immediately following this procedure the patient lapsed into stupor. The temperature rose to 103°F. and the pulse rate to 120. A lumbar puncture yielded xanthochromic fluid. The patient declined rapidly and died twenty-four hours later.

Necropsy findings. Brain. Gross. A tumor was found filling the posterior part of the third ventricle (fig. 10A). It measured about 1.5 cm. in diameter and consisted of a rather dense reddish mass encapsulated by a thin fibrous wall. The tumor proved to be an aneurysm of the left posterior cerebral artery. The exposed vessels at the base of the brain, aside from the aneurysmal wall, showed no sclerotic changes.

Microscopic anatomy. The pia-arachnoid was moderately thickened and infiltrated with large and small mononuclear elements, gathered mainly about blood vessels. Many of the cells contained pigment material and had acquired the char-

acter of macrophages. The aneurysm contained a well organized thrombus, through which recanalization had taken place. Between the vessel wall and the thrombus, at the periphery of the latter, there was a large collection of monocytes, most of which were macrophages containing pigment, debris and phagocytosed red blood cells. The intima showed a great irregularity in thickness, at some points it was exceedingly thick consisting mainly of a reticulum of connective tissue; in other places it was homogenized into a hyalin-like structure; at other points, again, it was entirely lost. The inner elastic membrane also showed great variability in thickness and alternately splitting, hypertrophy, atrophy or total disappearance. The media displayed advanced necrobiotic changes with the muscular coat at points being totally lost and replaced by granulation tissue. This was probably due to the closure of the vasa vasorum incident to the development of the aneurysm and the increased pressure within the lumen both interfering with the nutrition of the vessel wall.

Comment. This aneurysm occurring in a young person who manifested evidence of intracranial disease for about two years preceding the onset of the fatal illness, in all probability existed for some time before the onset of the earliest symptoms. The

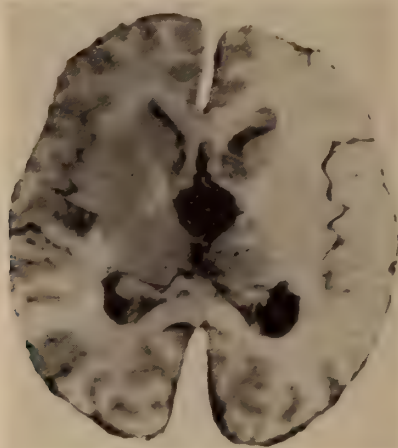


FIG. 10 (Case 9). Longitudinal section of the brain showing the aneurysm in the third ventricle.

fact that the meningeal signs were associated with xanthochromic cerebrospinal fluid and pleocytosis, indicates that oozing from a break in the aneurysm had occurred at the time the meningeal signs appeared. It is also probable that as the vessel became occluded by the thrombus the bleeding stopped. It is for that reason that no free blood and only xanthochromic cerebrospinal fluid was obtained on lumbar puncture. It may also be postulated that as the aneurysm had thrombosed, there appeared a new set of signs and symptoms, particularly those of increased intracranial tension, due to the obstruction caused by the aneurysm in the third ventricle.

Of interest is the fact that the so-called typical manifestations of aneurysm of the posterior cerebral artery, such as oculo-motor palsies, sensory disturbances or a Weber's syndrome were not present in this instance.

Case 10. Aneurysm of basilar artery, with signs suggesting (bulbar) encephalitis.

History (Adm. 315106; P.M. 7256). H. S., a young man, aged 17, was apparently well until three months before entering the hospital (June 16, 1930). At that time

he displayed some behavior alterations. About ten weeks later he swam a long distance, and shortly thereafter it was noticed that his voice had become hoarse and he was showing a tendency to hasten and slur his words. He himself noticed that on walking he would sway without a definite loss of sense of position. This symptom had abated to be practically absent for about three days, then there developed an indefinite sense of vertigo with no definite direction of rotation. A transient tic-like spasm in the left eyelid had been noted four days before admission to the hospital. He vomited once two days later and experienced some difficulty in swallowing, particularly solid foods. There had been some hesitancy in urination.

Examination. Slightly positive Romberg test. Speech was somewhat dysarthric. A bilateral lagging of external recti, horizontal and vertical nystagmus, a right facial asymmetry with the left palpebral fissure being larger than right were noted. The gag reflex was absent and the palate was paretic, causing regurgitation of food through the nose. There was slight pseudo-athetosis of the outstretched hands. The deep reflexes in the lower extremities were more active on the right.

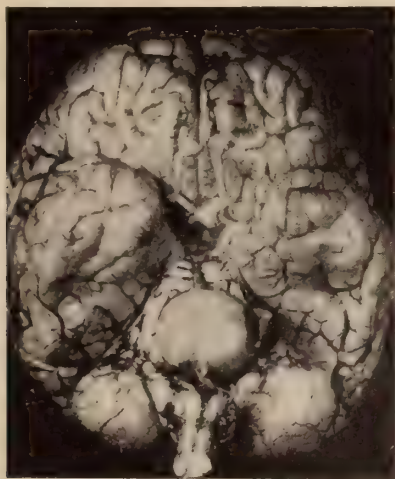


FIG. 11 (Case 10). Aneurysm of the basilar artery.

The abdominal reflexes were diminished and the cremasteric reflex was absent on the right side. There was a bilateral Babinski sign. There were zones of hyperalgesia from about C4 to D12 with diminution between and below these levels, involving all forms of sensation, but most marked for pain.

Laboratory data. Hemoglobin, 88 per cent. The cerebrospinal fluid obtained on the day of admission contained 40 mononuclear cells; on the day before death it contained 140 cells with 85 per cent monocytes and 15 per cent polymorphonuclear neutrophils.

Course. A diagnosis of encephalomyeloradiculitis was made and a course of typhoid vaccine injections was begun. He received two injections each followed by a chill and a subsequent rise of temperature to 102°F. The patient's condition became worse; he developed a pronounced bulbar palsy with greater difficulty in swallowing; speech becoming nasal. There appeared a definite left external rectus paresis with ptosis of the left upper eyelid. Typhoid vaccine therapy was then discontinued. The patient continued to do poorly, vomiting frequently and showing respiratory embarrassment. He died on June 16, on the tenth day in the hospital with respiratory paralysis preceding cardiac failure.

Necropsy findings. Brain. Gross. The surface of the brain was markedly congested. The convolutions were flattened and the sulci narrowed. On lifting up both frontal lobes a round tumor about the size of a plum and of a dusky blue color was seen lying under the pons (fig. 11). This tumor mass was connected posteriorly with the junction of the two vertebral arteries and anteriorly part of the basilar artery was seen to emerge from it. The pons showed a marked compression by the tumor. The latter was rather soft and compressible. The left trochlear nerve was found flattened and resting on the lateral wall of the depression made by the tumor. There was moderate symmetrical hydrocephalus. The vessels at the base of the brain, aside from the aneurysmal wall, showed no alterations.

Microscopic anatomy. Sections of the tumor showed it to be an aneurysm.

Comment. The youth of the patient is no longer considered as unusual for this type of lesion. The sudden development of bulbar symptoms after exertion deserves attention. The bulbar manifestations are readily explained by the relationship of the expanding lesion to the pons and medulla. It is this anatomical relationship with resultant manifestations of bulbar symptoms which was responsible for the diagnosis of encephalitis.

Case 11. Aneurysm of the basilar artery, simulating meningo-radiculo-encephalitis.

History (Adm. 300132; P.M. 6627). S. B., a man, aged 40, was admitted to the hospital on March 2, 1929 after a brief illness of eight days' duration, which had a sudden onset with severe headache, at first frontal and then generalized. The headache increased in severity and was accompanied by a mild rise in temperature and by persistent vomiting.

Examination. The patient was alert. There was a mild right central facial weakness, and the plantar response on the left was equivocal. The temperature was 102°F., the pulse rate, 72, and the respirations, 20. A lumbar puncture yielded cerebrospinal fluid which was at first bloody, and then in the process of removal gradually cleared up. The blood in the first tube was considered as traumatic in origin.

Course. On the second day in the hospital the patient developed moderate rigidity of the neck and a bilateral Kernig sign. A second lumbar puncture yielded clear cerebrospinal fluid, under pressure, with 90 cells per cubic millimeter, mostly lymphocytes. The blood pressure was 150 systolic and 110 diastolic. A blood count showed 9,700 white blood cells, with 85 per cent polymorphonuclear leucocytes. The patient's temperature rose to 103°F., and the pulse rate was 80. He was alternately drowsy and restless. There were constant myoclonic twitchings of the left side of the body. Despite the fact that smears of the cerebrospinal fluid had repeatedly failed to reveal any organism, a diagnosis of meningo-encephalitis was made, and intensive treatment with anti-meningococcus serum was begun. The third lumbar puncture, done on the fourth day in the hospital, yielded yellowish fluid with 2,400 cells per cubic millimeter, 90 per cent of which were polymorphonuclear leucocytes. The temperature continued elevated and varied between 103°F. and 104°F. Another lumbar puncture on the fourth day again revealed at first yellowish, turbid fluid, but at the end of the procedure the fluid became bloody. The latter was again considered of traumatic origin. The fluid in the first tube showed 4,200 cells per cubic millimeter, 85 per cent of which were polymorphonuclear leucocytes. Two days later, another lumbar puncture yielded frankly bloody fluid. The temperature and pulse rate continued to rise. That afternoon a combined lumbar and cisternal puncture was done, and bloody fluid was obtained from both sites. Through the lumbar puncture needle the fluid was dark brownish-red, while the cisternal puncture needle yielded bright red fluid. The patient grew rapidly worse and died six days after admission.

Necropsy findings. Brain. Gross. There was a moderate discoloration of the leptomeninges over the parieto-occipital region, due to the presence of blood in the subarachnoid space. At the base of the brain the cisterna pontis was filled with recently coagulated blood and the meninges showed a moderate degree of thickening. The vessels were unusually thin; the basilar artery, however, at 1 cm. posterior to its bifurcation into the posterior cerebral arteries, showed an aneurysm, spherical in outline, which measured about 0.5 cm. in diameter (fig. 12). It was covered by an opaque coating and was embedded in coagulated blood.

Comment. In this instance the age of the patient, the lack of previous history of cardiovascular disease, and the high cell count repeatedly found in the cerebrospinal fluid made it difficult to recognize the presence of an aneurysm during the clinical course. The discovery of definite arteriosclerotic changes in the vessels adjacent to the aneurysm and the histologic alterations in the brain and meninges

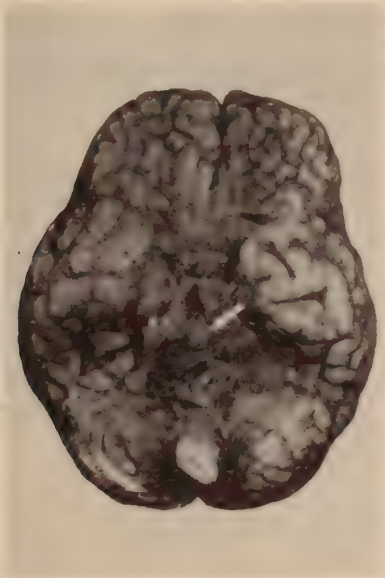


FIG. 12 (Case 11). Base of the brain showing the aneurysm of the basilar artery projecting through torn, but markedly thickened meninges. Arrow points to the aneurysm.

established definitely the arteriosclerotic origin of the aneurysm. The pleocytosis, which at the beginning led us to consider the case as one of meningitis and induced us to administer anti-meningococcus serum, is probably a reactive process and when it occurs, it creates diagnostic difficulties. In our experience no such pleocytosis occurs as a reaction to bleeding in the subarachnoid space.

Case 12. Aneurysm of basilar artery.

History (Adm. 380270; P.M. 9583). M. P., aged 43, was a married man. He was never seriously ill before. Five hours before admission, while sitting at the dinner table, he suddenly experienced a burning sensation in the right eye. Shortly thereafter he became dizzy and fell to the floor, but did not lose consciousness. He was unable to speak, and could not move the right side of his body.

Examination. The patient was acutely ill. The pupils were irregular but re-

acted to light and in accommodation. The fundi were negative. A shimmering nystagmus was present on right gaze. The left palpebral fissure was wider than the right. There was a motor aphasia, and a right hemiparesis, more marked in the face and arm. The deep reflexes were more active on the right side than on the left. A right Babinski sign was elicited and the right abdominal and cremasteric reflexes were absent. The blood pressure was 140 systolic and 90 diastolic.

Laboratory data. Blood: Hemoglobin, 115 per cent; white blood cells, 17,200, with 78 per cent polymorphonuclear neutrophiles and 20 per cent lymphocytes; blood Wassermann reaction, negative. Cerebrospinal fluid: 4 lymphocytes.

Course. On the second day in the hospital the patient developed a complete left hemiplegia and bulbar signs while the right hemiparesis was receding. Pulmonary edema set in and death occurred on the fourth day after admission. The clinical diagnosis was uncertain and thrombosis of a branch of the left middle cerebral artery; a pseudo-bulbar syndrome; a lesion of basilar artery; and multiple vascular insults, were all under consideration.

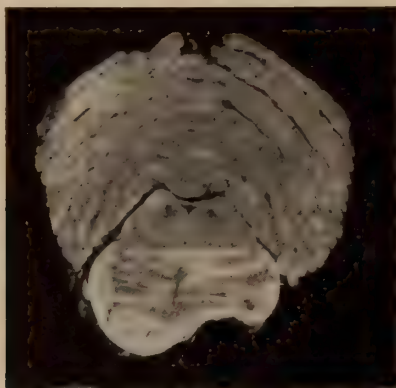


FIG. 13 (Case 12). Coronal section of the brain stem showing aneurysm of the basilar artery dislodged to one side, causing compression of adjacent part of the pons.

Necropsy findings. Brain. Gross. The arteries at the base of the brain were thin and elastic. The basilar artery at about the middle of the pons showed a circular dilatation about 1 cm. in diameter (fig. 13), covering the right half of the basal surface of the pons. There the pons felt softer than normal.

Comment. Of interest in this case as in other instances of basilar aneurysm is the absence of evidence of hemorrhage either into the substance of the brain or ventricular cavities. The clinical manifestations left the diagnosis somewhat uncertain, pointing, however, to the possibility of basilar artery thrombosis which is, of course, in keeping with the site of the vascular lesion.

Case 13. Aneurysm of vertebral artery with signs and symptoms suggesting angle tumor.

History (Adm. 421780; P.M. 10754). A. G., a woman, aged 50, entered the hospital for the first time in 1926, at the age of 36 to be treated for a post-partum sepsis and bronchopneumonia. She recovered completely and two years later passed through a normal pregnancy. The newborn, however, died when ten days old. One year later she had a miscarriage and since then no pregnancies. At the age of 42 (in 1932) she developed severe drawing pains on the left side of her neck and she became very

"nervous." At about the same time she had a mild episode of dizziness of a few seconds' duration. On investigation she was found to have hypertension, but nevertheless was treated for sinusitis, with the result that the pain in the neck was somewhat relieved. She soon, however, developed periodic headaches, most marked over the right supraorbital region. Shortly before her admission to the hospital she developed difficulty in swallowing and there was noted a change in the timbre of her voice and intelligibility of her speech. Generalized weakness set in and dizziness and insomnia became more frequent. She regurgitated food and had a feeling of fullness in her chest. "Drawing pains" in both calves made it difficult for her to walk or support herself. (She had had varicose veins for many years and was treated with injections and wore elastic stockings without relief.) Frequency of urination and nocturia had also developed. She entered the hospital for the second time on March 23, 1938.

Examination. The sense of smell was diminished bilaterally. There was bilateral exophthalmos. Bilateral papilledema and post-neuritic optic atrophy were present. There was horizontal nystagmus in both lateral planes. The left palpebral fissure was wider than the right. The corneal reflexes were bilaterally inactive; the jaw deviated to the left. There was some weakness of the left arm and leg with a bilateral tendency to pronation and convergence of the outstretched arms. The tendon reflexes were generally hyperactive but equal. The superficial reflexes were depressed. The vibratory sense was diminished in the lower extremities. The gait was broad-based and she dragged both legs, the left more than the right. The blood pressure was 165 systolic and 120 diastolic.

Laboratory data. The cerebrospinal fluid was clear, colorless, containing 3 cells and under an initial pressure of 108 mm. of water. The Ayala index was 5.5. The Pandy test was 4 plus. The total protein was 64 mg. per cent. X-ray examination of the skull revealed no evidence of increased intracranial pressure and a calcified pineal body was in normal position. X-ray examination of the sinuses showed no evidence of disease. Ventriculography revealed marked bilateral dilatation of the lateral ventricles, with the right being slightly larger than the left. There was no deviation from the midline and the third ventricle appeared dilated; the iter was visualized. Caloric tests were reported as follows: "The findings are suggestive of a posterior fossa lesion. The inward past pointing of the left hand and the failure to past point to the left on stimulating the left vertical canals suggest a lesion in the greater part in the left posterior fossa." A laryngoscopic examination disclosed a definite palatal paralysis.

Course. A subtentorial midline lesion was diagnosed, and a suboccipital exploration was attempted. It had to be discontinued for the patient passed into stupor in which she remained for several days. After a short period of slight recovery she declined again and died four days after the attempted craniotomy.

Necropsy findings. Brain. Gross. In the course of the removal of the brain a large bluish mass was found to compress the inferior surface of the cerebellum and the left half of the medulla and pons and seemed to extend into the foramen magnum (fig. 14). Upon removal, this mass, measuring about 1.5 x 1.0 x .75 inches was easily spilled out from the dell it had formed and found to be a large aneurysm of the left vertebral artery. It pressed into the pons pushing it upward and to the right and displaced the medulla and upper part of the cervical cord towards the right with a resultant marked deformity. The spinal accessory nerve was stretched over the mass. The vessels at the base of the brain, aside from the aneurysmal wall, showed no significant alterations.

On sectioning, the ventricular system was found to be markedly dilated as far as the posterior end of the aqueduct of Sylvius. At that point, the aqueduct was displaced to the right and reduced to an oblique narrow slit. The bed of the aneurysm

consisted of the left cerebellar hemisphere, with the pons above it and the medulla to the right. All of these three structures were compressed and somewhat displaced, but the medulla was the one which had suffered most. From the border of the pons down to the merge of the medulla with the spinal cord it was flattened and displaced to the right.

Microscopic anatomy. Sections of the left vertebral artery demonstrated a normal tunica adventitia and media. However, at one point in the lumen there is a proliferation of the cells of the tunica intima near its entrance into the aneurysm.

Comment. In this instance the aneurysm by its location, site and influence upon the structures surrounding the pontofacial angle, has strikingly simulated those of acoustic neuroma. The similarity was so close that it was only on post-mortem studies that the difference could be recognized. But even then there is little that could, now in retrospect, have helped in a clinical differential diagnosis. The suboccipital exploration carried out in the belief that an angle tumor would be found

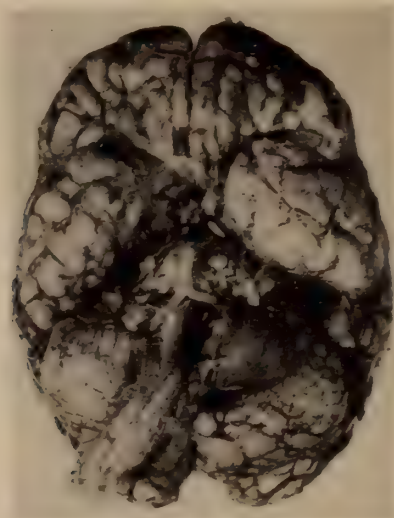


FIG. 14 (Case 13). The base of the brain showing aneurysm in the pontofacial angle.

was justified although it may have contributed to an earlier fatal termination. Were the patient's condition such as to allow full exposure and recognition of the lesion, the questions as to whether the removal of the aneurysm was possible could have been answered by the neurosurgeon.

COMMENT

It is quite obvious that this communication does not carry an encouraging message, but it was not its aim to bring unjustified optimism. The character of the material analyzed could do no more than disclose some of the discouraging features of cerebral aneurysms, features which received little recognition, much less than those of the somewhat more favorably situated and better preserved intracranial aneurysms.

It is disappointing that the cases in this series demonstrate the fact

that in a large number of aneurysms surgical intervention is almost impossible because of their location and origin from vessels supplying vital brain areas. This is particularly true of the basilar artery aneurysms, and to a large extent also for the aneurysmal sacs of the anterior communicating artery. Moreover, in a large group of aneurysms, damage to adjacent brain tissue and coincident changes in the aneurysmal wall are so advanced that surgical intervention does not only hold out little promise for any degree of recovery, but is also a most hazardous undertaking. In this connection it is essential to recognize that the disorganization-softening of brain tissue in the proximity of an aneurysm is due to interruption or marked retardation of its blood stream (as a result of thrombosis) to the affected area.

Another significant observation was made available through the study of the reviewed cases. It was shown that the tissue softening which takes place in the brain as the result of the effects of the neighboring aneurysm, is a stage which makes this area receptive to a subsequent effusion of blood from a ruptured aneurysm. Therefore, the blood under arterial pressure may then break through a narrow zone of necrotic tissue separating the area of encephalomalacia from the adjacent ventricular compartment. In this manner the ventricular system is flooded with blood leading to a fatal termination. This series of events is very similar to the one described by one of us (Globus (24)) in an earlier communication on massive cerebral hemorrhage. There too, it was found that an area of softening pre-existed the rupture of the intracerebral vessel, permitting the escape of blood into this potential cavity and from there through a defective zone of necrotic tissue into an adjacent ventricle.

It is not improbable that the anticoagulating properties of the cerebrospinal fluid which seeped into these defective (cystic) areas are in part responsible for the failure of the blood to clot early in the hemorrhagic process and thus spontaneously restrict the bleeding before it reaches a critical phase.

In the light of the clinical histories of our cases and of a number of other instances which came under the observation of one of us (Globus) it is quite apparent that the so-called spontaneous subarachnoid hemorrhage is usually the result of a ruptured aneurysm. It is also obvious that in cases of spontaneous subarachnoid hemorrhage, which present focal signs, such as pyramidal tract disturbances, aphasias, psychic disturbances and the like, the aneurysm has brought about massive disintegration of brain tissue. In such a situation the possibility of an eventual extension of a hemorrhage from a ruptured aneurysm into the ventricles is very strong.

Not all of the observations on the behavior of aneurysms and adjacent tissue are discouraging. The pia-arachnoid enveloping the affected vessel and the adjacent surfaces of the brain responds speedily to foreign bodies

by exudates and adhesions. Blood from a ruptured vessel provokes such a reaction causing the leptomeninges to form adhesions about the ruptured vessel and the brain in its vicinity. Therefore, under favorable conditions they are instrumental in holding back the current of blood from spreading and may eventually fully arrest the flow of blood from the defective vessel. This healing process may in many instances delay recurrence for months, years and as in one instance for many years (30 years in case 1).

Disquieting as the prognosis of cerebral aneurysm is, it nevertheless demands that its presence or absence be ascertained if the patient's condition permits of full investigation. It, therefore, invites the method of arteriography for its detection. By this means its size and situation can be ascertained and the advisability of surgical intervention can be carefully weighed, giving full consideration to other important factors such as the condition of the brain and the probable condition of the aneurysmal wall. This very method, on the other hand, by excluding the existence of an aneurysm may direct the attention of the examiner to other diagnostic possibilities, now open to more serious consideration, and perhaps, to such as holding out more promising therapeutic measures, as in the case of a brain tumor.

SUMMARY AND CONCLUSIONS

A review of the clinical and anatomical features in thirteen cases of intracranial aneurysms led to the following observations:

1. Intracranial aneurysms pre-exist a terminal fatal event by varying lengths of time. In some instances by as many as thirty years and probably longer.

2. In the great majority of instances the life history of an aneurysm is punctuated by two or more explosions characterized commonly by manifestations of subarachnoid bleeding.

3. A fatal issue usually results from rupture of the aneurysm and extravasation into an area of previously disintegrated brain tissue, ultimately leading to intraventricular hemorrhage.

4. In a few instances death is caused by the effect of the pressure expansion of the aneurysm without its rupture and without tissue disintegration.

5. Disintegration of brain tissue and hemorrhage into the areas of softening with extension into the ventricles is most commonly encountered in an aneurysm arising from the rostral part of the circle of Willis (anterior communicating, anterior cerebral and internal carotid arteries), while aneurysms of the posterior part of the circles (posterior cerebral, basilar and vertebral), exhibit manifestations of an expanding lesion.

6. Generalized cerebral arteriosclerosis was not common with the aneurysms in this series, there being advanced atheromatous changes in cerebral vessels of two cases, moderate changes in four and none at all in seven

instances of our series. This would point, as far as this material is concerned, to the significance of the congenital origin of aneurysms. Syphilitic and mycotic aneurysms were not among this series, indirectly indicating their rarity. The aneurysms were single in all but one case, in which they were multiple.

7. Hypertension was not a frequent accompanying condition, as it was found only in three of the thirteen cases.

8. The age distribution shows that fatal manifestations of an existing aneurysm usually appear during the third and fourth decade of life, but there is evidence that their silent existence precedes the fatal issue by many years. Aneurysms seem to be evenly distributed between the two sexes.

9. Clinically the aneurysms occasionally simulate the picture of brain tumor, encephalitis or vascular disorder of a less defined type; signs of increased intracranial tension, however, except headache, were found in few instances, and mainly when the aneurysm was more caudal in location; papilledema was rare; focal signs (often) of localizing character were frequent.

10. Convulsive seizures occurred and, in some instances, had a focalizing value, but when they were concomitant with bleeding into the subarachnoid space, they had no localizing significance.

11. Signs of meningeal irritation when present were indicative of subarachnoid bleeding. The cerebrospinal fluid was often bloody or xanthochromic, indicating recent or older bleeding. Occasionally a high leucocyte count was encountered in the cerebrospinal fluid, leading to the erroneous diagnosis of a septic meningitis.

12. The blood occasionally revealed a leucocytosis, usually found in the course of an episode of subarachnoid bleeding.

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STUDIES ON EXPERIMENTAL HYPERTENSION

XVI. THE EFFECT OF HYPOPHYSECTOMY ON EXPERIMENTAL RENAL HYPERTENSION*

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During the past few years the possible part played by the pituitary body in the pathogenesis of human hypertension has received the attention of various observers, notably Cushing (1). This has prompted the trial of radiation therapy directed toward this organ for the alleviation of the hypertension. In most cases of human hypertension treated in this way the value of irradiation of the pituitary body alone cannot be estimated because the adrenals were usually irradiated at the same time; but in those cases in which only the pituitary body was irradiated the treatment had no significant effect on the hypertension (2).

Not until the successful production in animals of persistent hypertension resembling human hypertension (3) was it possible experimentally to evaluate the part played by the pituitary body in the pathogenesis of elevated blood pressure. Page and Sweet (4), as a result of their investigations in a series of dogs, concluded that "Preliminary hypophysectomy does not prevent the rise in blood pressure established by renal ischemia but the rise tends to be transient. Hypophysectomy in dogs with hypertension produced by renal ischemia reduces arterial hypertension to about normal levels. It appears to reduce slightly the blood pressure of normal dogs." The seeming inconsistency of their results in the treatment and prevention of experimental renal hypertension by hypophysectomy made it desirable to repeat at least one phase of this investigation.

It was thought that if it could be shown definitely that hypophysectomy does not prevent the development of the benign and malignant phases of experimental renal hypertension, and especially if the benign phase of the hypertension were to persist for a long time, then the conclusion would be justified that the hypophysis does not play a significant part in the pathogenesis of this type of hypertension. Since this latter closely resembles human so-called essential hypertension so frequently associated with vas-

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cular disease of the kidneys, the application of the experimental results to human hypertension would also be justifiable.

EXPERIMENT

Ten dogs were subjected to hypophysectomy under visual guidance, according to the method of Sweet (5). A variable period after presumably complete hypophysectomy, either the main artery of both kidneys was permanently constricted by a silver clamp or one main renal artery was first constricted and later, when the blood pressure was elevated, the other kidney was removed. Both procedures, when carried out on normal dogs, usually result in persistent hypertension (3).

TABLE 1

	NUMBER OF DOG	MAXIMUM BLOOD PRESSURE*			LENGTH OF HYPERTENSIVE PERIOD
		Normal period	Period after hypophysec- tomy	Period after constriction of renal arteries	
		<i>mm. Hg.</i>	<i>mm. Hg.</i>	<i>mm. Hg.</i>	<i>months</i>
Completely hypophy- sectomized	4-81	135	130	195	23
	5-16	140	145	240	9
	5-20	135	135	240	6
	5-24	140	130	245	10
	5-28	155	155	215	18
Incompletely hypo- physectomized	4-85	115	100	170	5
	4-95	150	140	220	15
	5-17	170	165	255	5
	5-21	130	135	200	5
	5-29	110	90	195	10

* "Mean" femoral blood pressure determined by the direct method.

The results (see table 1) show clearly that in what proved to be five completely hypophysectomized animals (4-81, 5-16, 5-20, 5-24 and 5-28) the blood pressure not only became elevated but remained at persistently high levels for many months. In these five animals, no remainder of hypophysis was discovered in the gross examination at autopsy, and none was found by careful microscopic examination of the tissue at the base of the brain in the region of the stalk of the pituitary body.

In five dogs (4-85, 4-95, 5-17, 5-21, 5-29) the hypophysectomy was not complete. In two of these dogs (5-17, 5-21) a remnant of hypophysis was recognized in the gross, and in two others (4-85, 4-95) pituitary tissue was discovered by microscopic examination of the brain in the region of attachment of the pituitary body. In the fifth animal, (5-29) because the autopsy was performed 48 hours after death, the brain was in such a state of post mortem decomposition that a satisfactory examination for a rem-

nant of hypophysis was not possible. For this reason this animal is grouped with those that were not completely hypophysectomized.

Table 1 shows that in the completely hypophysectomized animals the maximum blood pressure reached levels just as high as in the group in which a remnant of hypophysis was found and it was actually as high as in hypertensive animals with hypophysis intact (3). In the completely hypophysectomized animals the hypertension persisted for at least as long a time as in the other group.

Figure 1 (Dog 5-24) shows that constriction of both main renal arteries was sufficient to keep the blood pressure considerably elevated for more than five months, and the hypertension undoubtedly would have continued longer had the experiment not been terminated.

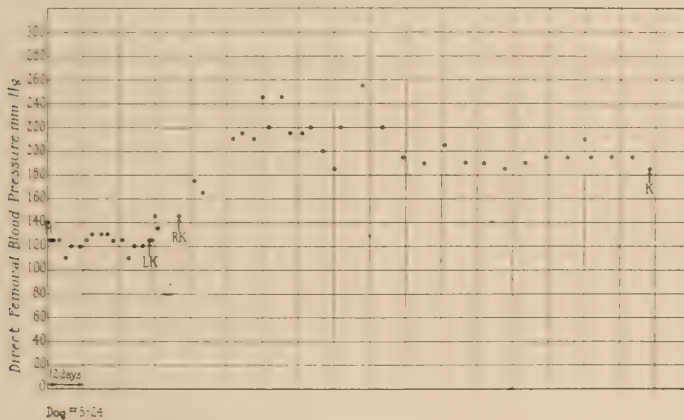


FIG. 1. Dog 5-24. Male, middle aged, chow, weight 11 kg.

- II = Complete hypophysectomy.
- LK = Moderate permanent constriction of left main renal artery.
- RK = Moderate permanent constriction of right main renal artery.
- K = Killed.

Figure 2 (Dog 5-20) shows that it was necessary to increase the constriction of the left main renal artery (LKC), later to excise the right kidney (LN) and finally to place a cellophane bag (L Cel) around the left kidney in order to keep the blood pressure elevated in this dog. The animal finally developed renal excretory insufficiency and died in uremia. At autopsy, it exhibited all the signs of the malignant phase (6, 7) of this type of hypertension. Microscopically, the typical lesions, petechiae and fibrinoid degeneration, necrosis and necrotizing acute inflammation of arterioles were present in various organs.

In Dog 5-16, (fig. 3), in which it was necessary to carry out similar procedures to those performed on Dog 5-20 in order to make the hypertension persist, renal damage was evidently not excessive, renal excretory insufficiency did not develop and this animal did not show any of the signs of the malignant phase, although the blood pressure was very high.

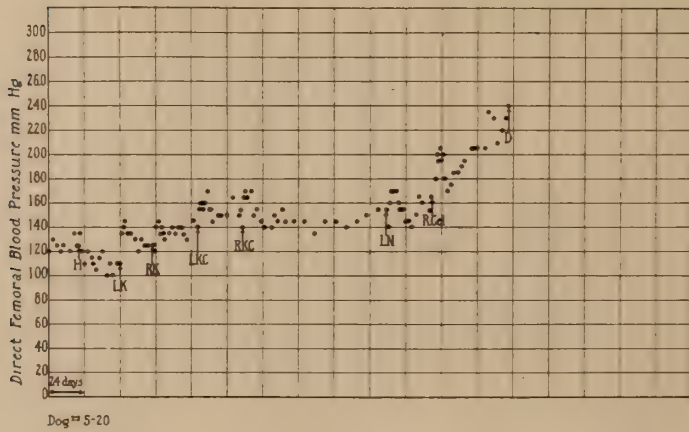


FIG. 2. Dog 5-20. Male, young, spaniel, weight 13.6 kg.

- H = Complete hypophysectomy.
 LK = Moderate permanent constriction of left main renal artery.
 RK = Moderate permanent constriction of right main renal artery.
 LKC = Left main renal artery occluded.
 RKC = Right main renal artery occluded.
 LN = Left nephrectomy.
 R Cel = Right kidney wrapped in cellophane.
 D = Died

Terminally this animal became uremic. The day before death, B.U.N. 127.5 mg., creatinine 9.6 mg. and CO_2 47 volumes per 100 cc. blood. The animal showed the typical gross and microscopic arteriolar lesions of the malignant phase.

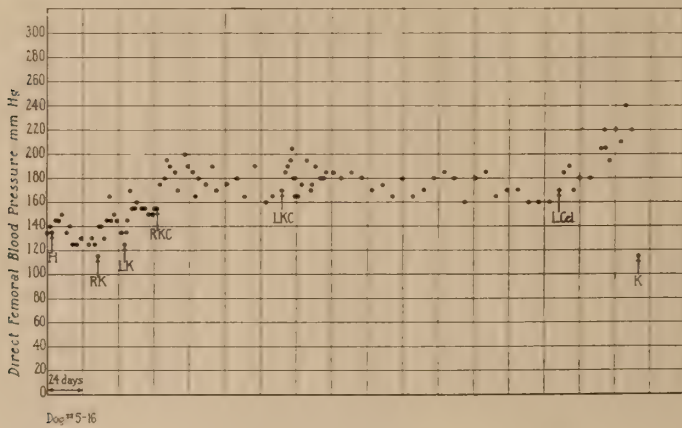


FIG. 3. Dog 5-16. Mongrel, make, middle aged, weight 6.4 kg.

- H = Complete hypophysectomy.
 RK = Moderate permanent constriction of right main renal artery.
 LK = Moderate permanent constriction of left main renal artery.
 RKC = Right main renal artery occluded.
 LKC = Left main renal artery occluded.
 L Cel = Left kidney wrapped in cellophane.
 K = Killed.

In Dog 4-81 the blood pressure was still significantly elevated when the animal was killed 23 months after the first main renal artery was constricted. In this dog too it was necessary later to increase the constriction of both main renal arteries in order for the hypertension to persist. At autopsy there were no signs of the malignant phase of hypertension in this animal.

Figure 4 (Dog 5-21) is shown merely to illustrate the finding that in one of the incompletely hypophysectomized animals the level of the blood pressure as a result of constriction of both main renal arteries was no greater than in the completely hypophysectomized animals.

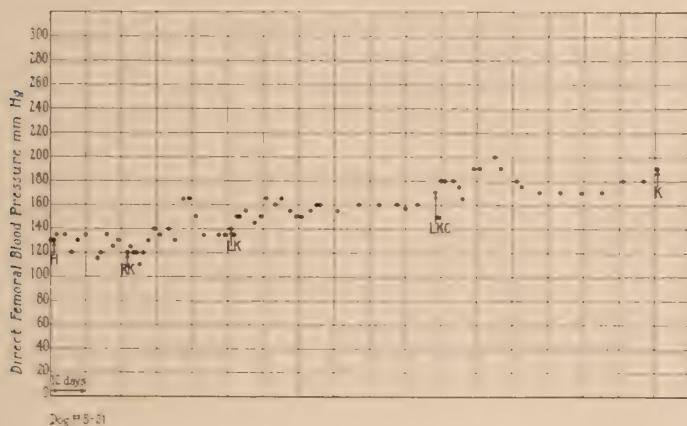


FIG. 4. Dog 5-21. Dachshund, male, middle aged, weight 11.8 kg.

- H = Incomplete hypophysectomy.
- RK = Moderate permanent constriction of right main renal artery.
- LK = Moderate permanent constriction of left main renal artery.
- LKC = Left main renal artery occluded.
- K = Killed.

A microscopic examination was also made of the tissues of the completely hypophysectomized animals in the benign phase of experimental renal hypertension. The only significant anatomical changes found in these animals were unusually small, but anatomically normal adrenals and a thickened media in the small arteries and arterioles of many organs in those animals in which hypertension had persisted for a long time. There was no sign of arteriolosclerosis or of any pathological change other than the medial hypertrophy in any of the arteries or arterioles of the animals in the benign phase of hypertension.

SUMMARY AND CONCLUSIONS

In agreement with Page and Sweet it has been shown that complete hypophysectomy does not prevent the development of experimental renal

hypertension and that it tends to lower slightly the blood pressure of normal animals. In the hypophysectomized animals that did not develop renal excretory insufficiency (the benign phase) the hypertension persisted at high levels for a long time. The malignant phase of this type of hypertension was also observed in an animal that had been completely hypophysectomized. This rules out the hormones of the pituitary body as playing a significant part in the pathogenesis of the arteriolar lesions observed in the organs of animals in the malignant phase of the hypertension.

The effect of any surgical procedure, including hypophysectomy, on established experimental renal hypertension must always be evaluated with caution because in some hypertensive animals, even without any type of treatment, there is a tendency for the blood pressure to reach lower levels. It is considered, therefore, that more significance should be attached to the finding that experimental renal hypertension cannot be prevented by hypophysectomy than to the effect of this procedure on previously hypertensive animals.

The results of this study lend no support to the view that the hypophysis plays a significant part in the pathogenesis of experimental hypertension due to constriction of the main renal arteries or of any similar type of human hypertension and offers no justification for surgical or other interference with the integrity of the pituitary body for the treatment of any type of human hypertension that resembles experimental hypertension of renal origin.

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DEVELOPMENT OF KNOWLEDGE CONCERNING THE MEASUREMENT AND RHYTHM OF THE PULSE

(HEROPHILUS, GALEN, CARBOLIENSIS, STRUTHIUS, GALILEO, FLOYER)

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In a previous paper I have presented briefly the earliest known historical material dealing with the heart and circulation which has come down to us from Antiquity, particularly from Egyptian and Greek sources. These contributions, starting with the earliest known reference contained in the Edwin Smith Surgical Papyrus (3000 B.C.), have increased progressively, with ever deepening understanding and changing concepts. They may be found in, and have been collected from, the following writings: the Ebers Papyrus (2000–1500 B.C.), Hippocrates (460 B.C.) Aristotle, (384–322 B.C.), Praxagoras (340–320 B.C.), Herophilus (ca. 330–300 B.C.), Erasistratus (330–250 B.C.).

In the present paper I propose to discuss somewhat more fully contributions particularly concerning the pulse, its measurement and rhythm, contributions which, with the exception of Herophilus', considered the first firm foundations of ancient pulse lore, have all appeared during the Christian Era and to a large extent have continued in medicine until recent times.

Herophilus' significant contribution of the use of the water clock (Clepsydra) for counting the pulse, the first use of an instrument of precision in medicine, and his development of a quantitative theory of the pulse, has been amplified and discussed in considerable detail in two classical papers—the one by Marcellus—"a little treatise of no earlier date than the second century"—the other by K. F. H. Marx in 1838. Marcellus points out that Herophilus' interest in pulse counting was primarily "to appraise the evidences of fever," and by calibrating the water clock for various normal age groups and varying pulse rates in control individuals, he reached his goal. Herophilus apparently placed so much importance on the pulse rate as a constant, and as an index of the general health or disease of the body, that "on the occasion of a visit to a patient, he set up the water clock at the bedside, palpating and counting the pulse," and made his deductions accordingly.

Schöne, in commenting on the water clock, believed that "Herophilus

¹ Deceased, June 27, 1941.

classified the pulse rhythm in four age groups, and as only a single water clock is mentioned for the observation of patients of varying ages and varying pulse rates, concluded that the instrument could be regulated."

The introduction of the Clepsydra as an instrument of precision at this early date seems of great significance, for which reason I am translating Schöne's description of the method as follows:

"By the water clock one is enabled to estimate the period of time during which a known quantity of water flows from one vessel to another placed below. The passage of time may be estimated by observing either the outflow or inflow vessel. Herophilus noted the time in which the lower vessel had become completely filled. At a minimum four time periods could be measured, by varying the size of the lower vessel. A second method of varying the capacity was by the introduction or removal of wax within either the outflow or inflow vessel."

Marx credits Herophilus as the first to appreciate the significance of the pulse as an index of health and disease and as observing and differentiating such decisive pulse variations as size, rate, strength and rhythm, particularly evaluating the last from the standpoint of prognosis.

Viewed from the modern perspective and at this long range, one confesses to considerable difficulty in understanding the significance of Herophilus' use of the word "rhythm," described as the "metrical" portion of his pulse lore. In this connection Osler points out that Herophilus was greatly influenced by the musical theories of his time, comparing the rhythm of the pulse to musical rhythm, and giving them specific names such as the "goatlike" or bounding pulse, *pulsus capricious* or *deciotus* (Rosenbloom).

In an interesting paper entitled "Primitive Methods of Measuring Time," R. W. Sloley likewise discusses the Clepsydra—a "water thief"—as a distinctive method based on the flow of water, the oldest specimen of the water clock dating from about 1300 B.C. An unusually fine specimen of an Egyptian outflow water clock of about the time of Herophilus is in the museum of the Oriental Institute of the University of Chicago. In contemplating the use of such an instrument for counting the pulse one is impressed, among other things, by its lack of portability and the calibration for relatively large intervals of time—hours. It would have seemed desirable, if not probable, that Herophilus must have used a less cumbersome "water thief"—and one of a somewhat finer calibration!

Much of Herophilus' metrical studies of the pulse was criticized by Galen some 400 years later. Galen, born at Pergamos 130 A.D.—

"the greatest name after Hippocrates in Greek medicine, in whom was united as never before, and indeed one may say never since—the treble combination of observer, experimenter, and philosopher,"

likewise criticized Hippocrates for his lack of interest in the arterial pulse, insisting that the subject was not adequately studied until after his time.

"He was first in the history of biology to appeal to experiment for an answer to questions confronting him, and he may in consequence be referred to as the founder of experimental physiology."

Galen's major contribution to the pulse occupied some 200 folio pages contained in sixteen books, with titles and subdivisions as follows (Coxe):

- II Galeni, De pulsibus libellus ad tyrones, (a concise treatise on the pulse for students);*
- III Galeni, De pulsuum differentiis (on the differences of pulses), 4 books;*
- IV Galeni, De dignoscendi pulsibus (on the knowledge of the pulse from books), 4 books;*
- V Galeni, De causis pulsuum, (on the causes of the pulse), 4 books;*
- VI Galeni, De praesagatione ex pulsibus, (on prediction from the pulse), 4 books;*
- VII Galeni, Synopsis librorum, suorum, sexdecim de pulsibus, (general summary).*

Coxe, an opponent of Harvey, thus succinctly comments on Galen's pulse study:

"Upon the whole on reviewing the sixteen books of Galen on the pulse at large . . . I apprehend we may safely conclude that there is fully as much good sense and reason in his speculations as in any of those that have since his time been promulgated by Solano, Bordeau, Nihill, Falconer, and others down to the later period of Hillier, Parry, and many others in Great Britain and elsewhere."

Galen's astuteness of observation, as well as his wide experience as a clinician, is well exemplified by an anecdote recounted by Osler, an early example of insight into the "total personality" and a remarkable contribution to the role of the emotions in pulse rate and rhythm:

"Called to see a lady, he found her suffering from general malaise without any fever or increased action of the pulse. He saw at once that her trouble was mental, and like a wise physician engaged her in general conversation. Quite possibly he knew her story, for the name of a certain actor, Pylades, was mentioned, and he noticed that her pulse at once increased in rapidity and became irregular. On the next day he arranged that the name of another actor, Morpheus, should be mentioned, and on the third day the experiment was repeated without effect. Then on the fourth evening it was again mentioned that Pylades was dancing, and the pulse quickened and became irregular, so he concluded that she was in love with Pylades!"

So far as I am aware, this is the first recorded instance of a simple tachycardia with extrasystoles emotional (psychogenic) in origin!

Few contributions of note were added to the exhaustive pulse studies of Galen for nearly 1000 years, at which time Aegidius Carboliensis of the Salernitan School, writing in metrical form, described in his "De Pulsibus" fifteen or more varieties of the pulse. Known as a distinguished French physician and humanist, Carboliensis studied at Salerno and wrote medical poems in Leonine verse, which were considered of great importance as being the main channel through which Salernitan lore reached the Parisian physicians. Flint translated the headings under which Carboliensis wrote his short pithy verses as follows:

"Concerning the Pulse and its Sizes: On a large pulse; In what does a large pulse consist? Definition of a small pulse; strong or weak pulse; slow or fast pulse; hard or soft pulse; empty or full pulse; hot or cold pulse; frequent or rare pulse; pulsus deciduus; equal pulse; unequal pulse; irregular pulse."

(Flaxman.) In these verses, descriptive of the many varieties of the pulse, one senses a remarkably close approximation to our modern clinical classification, the result of the painstaking and methodical observations of our able clinicians of 25 to 50 years ago—observations made just prior to and including the clinicians of James Mackenzie's generation, and the introduction of graphic and electrical methods of pulse registration.

Another 400 years elapses before we find a still more elaborate and intricate classification of the pulse, by the Polish physician, Josephus Struthius, with, for the first time, the publication of figures of pulse waves. Struthius, born in Posen in 1510, best known for his translation into Latin of the writings of Galen, refused Philip II of Spain's glittering offer to become attached to his palace—accepting instead the post of "Leibarzt" to King Sigismund August of Poland.

The title page of Struthius' most famous publication, "Artis Sphygmica" (1555) and a diagram of variations in the character of the pulse found in different areas of the palmar surface of the hand, with descriptive terms such as "celer," "tardus," etc., still found in modern clinical nomenclature, and the elaborate, complex table of the countless varieties of the pulse described by Struthius, which is found folded within the early pages of his book testify to the industry and thoroughness of this first graphic study of the pulse—antedating some four centuries our modern arterial and venous pulse tracings,—electrocardiograms, etc. Perhaps, gauged by such perspective, one may be forgiven the role of prophecy by predicting that sometime within the next 400 years our medical descendants will present to the scientific world equally revolutionary and seemingly radical discoveries and contributions to our present day knowledge and concepts of the circulation!

Shortly after the death of Struthius, the young physicist-astronomer

Galileo, the "wrangler," about a year after his matriculation, questioning among others the dictates of Aristotle, made his first discovery, that of the synchronism of the oscillation of the pendulum, timing the excursions of his pulse. This was the first attempt at accurate measurement of any

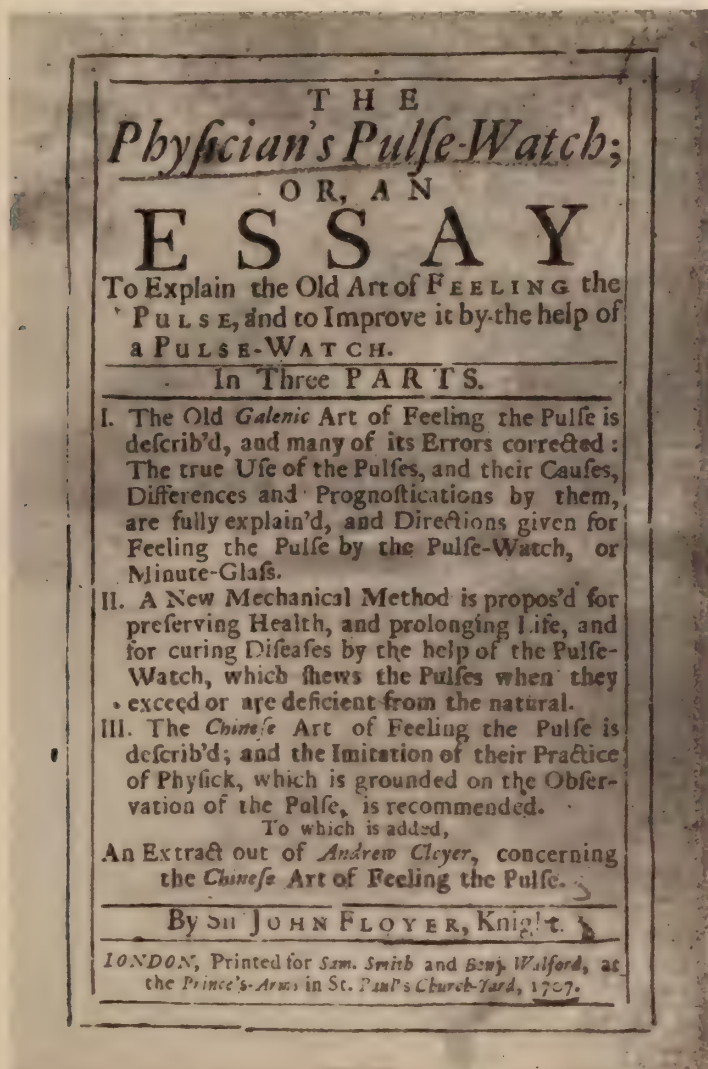


FIG. 1

bodily function, as well as the basis of the modern clock. He was not, however, then thinking of clocks, but only of the construction of an instrument which should mark with accuracy the beat of the pulse and its variations from day to day. He quickly gave form to his idea, and it was wel-

comed with delight by physicians and was long in general use under the name of "Pulsilogier" (Charles Singer).

Another important contribution which must be recorded in this brief summary of the history of the measurement and rhythm of the pulse is that of the invention by Sir John Floyer of the minute watch, occurring approximately at the time of Harvey's momentous discovery of the circulation. Sir John Floyer (1649-1734) studied philosophy and medicine at Oxford, later practising medicine at Lichfield. He noted the relation of the frequency of the pulse to that of respiration, and introduced the minute watch to determine the pulse rate. His now well known book on the Physician's Pulse Watch contains the following title page statement (fig. 1).

"The old Galenic art of feeling the pulse is described and many of its errors corrected. The true use of the pulses and their causes are fully explained and directions given for feeling the pulse by the pulse watch or minute glass."

In the "Preface" a somewhat more complete statement of the circumstances of its invention is given. It is interesting to note that Floyer refers to the old Galenic art of feeling the pulse, apparently unaware of the earlier observations of Herophilus. Schöne has also pointed out that Herophilus' observations on the pulse did not survive antiquity and were again lost sight of for many centuries. On the other hand Floyer's reference to pendulum clocks doubtless evidences his awareness of Galileo's invention and introduction of the Pulsilogier.

In conclusion I should like to quote Floyer's philosophical "reflexions" on the "Pulses in England":

"If the Pulses in England be in a

Minute—70

In a quarter of an hour there will be—1050

In an hour—4200

In 24 hours—100800

For 70 Pulses in a minute there are 14 respirations.

In 24 hours the Respirations are 20160

In an hour the Respirations are 840.

I hope these surprising numbers will produce the same Reflexions in the Reader as I shall now make. That nothing but an infinite wise God could control such perpetual and numerous Motions as the Pulse and Respirations have in one Day; but it requires the Providence of the same wise Creator to preserve 'em all the Days and Years of our Lives. Our Lives are measured by the Number of our Pulses, the first Pulse begins Life and it ceases with the last; if the Number of one Day be wonderful, the many Millions which will happen in one Hundred Years ought to be considered the greatest Miracle of the Creation."

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VASCULAR ALLERGY. II

MANIFESTATIONS OF POLYVALENT SENSITIZATION

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The allergic manifestations in man are attributed primarily to tissue edema. According to Lewis (1) and Dale (2) the latter is the result of an antigen-antibody interaction on or within the cell with the release of histamin-like substances which lead to increased vascular permeability. Histological observations by Fröhlich (3) and Rössle (4) support this view. In their description of the genesis of the Arthus phenomenon in the mesentary of the sensitized frog following local application of hog serum, they describe capillary stasis, engorgement of capillaries with plasma and emigration of leucocytes accompanied by distinct edema of the contiguous nerves. The Arthus phenomenon in the guinea pig produced by sensitization with various proteins such as horse serum, eggwhite, etc. is characterized by edema; in the rabbit by severe necrosis. This lesion, according to Menkin (5), is marked by increased permeability of the capillaries, outpouring of fibrinogen into the tissue spaces with deposition of fibrin and thrombosis of the lymphatic capillaries and small veins which insures the local fixation of antigen. The initial implication of the endothelium of blood vessels rather than smooth muscle in this reaction is obvious. Moreover primary sensitization of smooth muscle of human origin like that which exists in the lower animals, has not been demonstrated in man. Since, therefore, the blood vessels appear to be the primary seat of the allergic reaction, it may be reasoned that any tissue in the body may become sensitized i.e. "shock organ" provided the blood vessels supplying it are sensitized.

The simplest example of this is urticaria or eczema due to food hypersensitiveness, in which the skin becomes a shock organ by virtue of sensitization of the blood vessels which supply it. Should, however, the sensitization be concentrated in the vessels themselves it is readily conceivable that pathological changes may arise in the vessel walls and may lead to various secondary changes in the tissues which they supply depending upon the resultant anoxemia and allied factors.

The elements involved in the development and localization of allergic manifestations in man are many. The first is the constitutional factor, which accounts not only for the inheritance of the allergic state but also for the character of the shock tissue. Thus, for example, the child of an

asthmatic parent is apt to develop respiratory allergy while another, in whose family gastro-intestinal or skin manifestations occur, may become subject to similar disturbances. It is well established that about 50 per cent of patients with asthma or hay fever give a personal and family history of allergy. They not only have positive skin reactions to the incriminating allergens, but corresponding antibodies in the blood stream called *reagins*, demonstrable by passive transfer. These individuals are designated by Coca as "atopic." Other patients with clinical manifestations identical with those seen in the atopic individual may not have any personal or family histories of allergy but, nevertheless, their presenting symptoms are recognizable in accordance with the immunological criteria applicable to the atopic state. It has been shown also that so-called normals, depending upon the degree of their receptivity and the character of the antigenic stimulation, can be sensitized by foreign proteins with the production of reagins, just as the atopic individuals. The difference between the two, however, is explained by the fact that the atopic patient has a tendency to polyvalent sensitivity with multiple clinical allergic manifestations which may appear simultaneously or alternatively, such as asthma and eczema, greater intensity in his response and a more consistent presence of blood reagins, corresponding to the reacting substances, in contrast to the so-called normal.

The second important factor in the allergic reaction is the nature of the exciting agent or allergen. There seems to be an affinity between certain allergens and the affected tissue i.e. shock organ. Pollen for instance will induce respiratory more often than gastro-intestinal symptoms. One may, therefore, expect that unless there is such an inter-relationship the mere presence of an allergen in the environment will not be followed by symptoms usually induced by that particular protein substance. In other words given an allergic individual plus sufficient exposure to a specific allergen there must be present a receptive shock tissue before reactions will follow.

While the nature of the shock organ may be influenced by hereditary factors it may also be developed in the so-called normal as well as the atopic individual through the medium of many non-specific agents of chemical, physical, or bacterial origin. The physiological changes wrought by such agents may so alter the reactions of the affected tissues that they become readily sensitized by allergens to which they were previously impervious. This is best illustrated by such examples as hyperergic reactions in the cardiovascular system of the sensitized animal following administration of epinephrine, caffeine or alcohol, (Knepper and Waaler (6)) or in joints and adjacent tissues after refrigeration and trauma, (Vaubel (7), Lasowsky and Kogan (8)). It is also demonstrable in the Shwartzman (9) phenomenon. Here rabbits sensitized with horse serum and injected locally with a bacterial product, such as *B. coli* toxin, respond in the prepared site with hemorrhagic necrosis on intravenous reinjection of horse serum.

Such a local response does not ordinarily follow reinjection of horse serum in the sensitized animal but does appear if the animal, previously "prepared" locally with *B. coli* toxin, is reinjected intravenously with the homologous toxin, or a heterologous toxin capable of inducing similar hemorrhagic reactions. The creation of a shock organ formerly called a "*locus minoris resistentiae*" by older clinicians, by the various methods referred to, is sometimes called non-specific allergy and is important in the development of disease processes. Non-specific factors may not only play a rôle in the localization of the lesion but, may also as in the case of bacterial products by virtue of their toxic effects, enhance the action of a sensitizing agent. Thus they may change the relatively simple reversible allergic reaction into a more intense and irreversible one, both in the atopic and non-atopic individual. The non-specific agents need not necessarily be exogenous, but may be inherent in the allergen responsible for the primary sensitization. Thus, for example, hypersensitiveness to coffee carries with it sensitization to the protein in the coffee bean as well as to the pharmacological effects of caffeine. Sensitization to tobacco incorporates with it the simultaneous toxic effects of nicotine. The vasoconstriction induced by nicotine is the same in man and animal whereas the allergic effects of tobacco differ considerably in various individuals. When dealing with a complex substance as tobacco, the synergistic effects of nicotine and tobacco protein which follow sensitizations to the latter, or possibly to both components, may be compared to the summation effects which result from combined sensitization to pollen and bacterial agents, or food and drugs simultaneously. A person sensitive to these combined allergens may have respiratory symptoms, gastro-intestinal and possibly skin manifestations all at once or in succession.

In dermatology the synergistic effects of drugs and bacteria or other allergens are well known. Thus, Milian (10) and other French dermatologists describe the interaction or synergism between drugs and bacteria wherein the development of symptoms simulating infectious diseases following the ingestion of drugs are due not only to the drug hypersensitiveness, but also to the potentiating effect of the drug upon some dormant infectious agent. While this may be true for drugs it also holds for foods, pollens and other inhalants. Such a mechanism, however, does not exclude the fact that drugs, foods, or for that matter any other allergen in and of themselves can induce clinical pictures identical with many infectious processes.

While these mechanisms have been studied to a certain extent in conjunction with diseases of the skin and the respiratory apparatus, very little has been done in investigating their rôle in relation to the cardiovascular system. In dealing with diseases affecting the heart and blood vessels, the criteria established for the diagnosis of recognized allergic diseases must serve as a point of departure. Thus it is highly important to study the

development and course of cardiovascular disease as it appears in the atopic, whose constitutional background is so significant in his reaction to his environment and disease, as well as in the so-called normal individual capable of acquiring sensitization. Here, as in asthma, if an allergic mechanism is concerned in the evolution of disease of the vascular system, the process may be found to be reversible or irreversible, and the exciting cause, as in other forms of allergy, may be discovered in foods, inhalants, drugs, bacteria, or combinations of any of these. The following cases illustrate these points.

CASE REPORTS

Drug allergy. Purpura due to aspirin sensitization.

Case 1. History (Adm. 464064). R. C., aged 64, was admitted to the medical service of Dr. George Baehr, October 18, 1940, with a history of having had gonorrhea and syphilis at the age of 18. In 1917 he was found to have a positive Wassermann reaction and tabes dorsalis. During the next twenty years he was treated with arsphenamin, bismuth and iodides at the Out-Patient Department of The Mount Sinai Hospital. In view of repeated negative Wassermann reactions, therapy was discontinued in 1932. The shooting pains in the legs and ankles persisted despite all previous treatment. In order to relieve them the patient took 1 to 5 grams of aspirin a day for 23 years. For three weeks prior to admission, because of increasing severity of the pains, the patient took 3 to 5 grams of aspirin per day. Six days before entry into the hospital he developed mild diarrhea, which was followed by a rash, chills and fever.

Examination. He was found to have a temperature of 102°F., moist râles at both bases, moderate enlargement of the heart to the left with a systolic murmur at the apex. The blood pressure was 170 systolic and 90 diastolic. The liver was felt 2 to 3 fingers-breadths below the costal margin. The most significant finding was an extensive purpuric eruption over the entire skin of the neck, both legs, the palms, soles, penis and scrotum. There was also slight edema of both legs.

Laboratory Data: Hemoglobin, 69 per cent; red blood cells 3,750,000; white blood cells, 9,200; polymorphonuclear leucocytes, 70 per cent; 18 per cent non-segmented; lymphocytes, 23 per cent; mononuclear cells, 3 per cent; and 3 per cent eosinophiles. Tourniquet test was positive. The bleeding time was 8 minutes, clotting time 4 minutes, and a good clot retraction in 4 hours. The platelet count was 200,000. Sedimentation time was 30 minutes. The stool showed a 4 plus guiac reaction. The blood culture was negative. The blood Wassermann reaction was also negative. Various serologic tests to determine the cause of the diarrhea were negative. The x-ray examination of the colon disclosed no abnormalities.

Course. In the ensuing one and a half weeks the salicylates were discontinued. The temperature fell to normal and the diarrhea, which amounted to 7 to 8 loose bowel movements a day, gradually subsided. The purpuric eruption faded and the tourniquet test reverted to normal. In order to determine the relationship between the purpura and the salicylates the patient was given 15 grams of aspirin. Within 24 hours the purpuric rash returned and the tourniquet test became positive. The bleeding time and coagulation time were not altered. The guiac reaction in the stool was likewise negative. The aspirin was discontinued and the purpura disappeared. Skin tests with aspirin were negative. A provocative test with sodium salicylate led temporarily to a positive tourniquet test.

Comment. A known syphilitic, who in spite of continuous antiluetic treatment and a negative Wassermann reaction continued to have tabetic crises. Apparently he was not cured of the underlying disease. The ingestion of large amounts of aspirin over a long period of years sensitized him to the drug resulting in the production of purpura, as repeatedly proven. The purpura and the positive tourniquet test clearly indicated involvement of the capillary vessels as a shock organ. The diarrhea and the positive guaiac test in the stool could be attributed to purpura in the intestinal wall. The coincident disappearance of the blood from the stool and purpura of the skin would tend to support this concept. Whether the intensity of the vascular reaction was due to a synergistic effect of the liberated syphilitic products and the aspirin, is a question which must be borne in mind.

Tobacco allergy. Thrombo-phlebitis migrans and thrombo-angiitis obliterans.

In a series of reports beginning in 1932 I described the presence of positive skin reactions to tobacco in cases suffering from thrombo-angiitis obliterans, certain types of migrating phlebitis and angina pectoris with or without coronary artery disease. Of 140 patients with thrombo-angiitis obliterans studied, 95 cases or 78 per cent showed positive skin reactions to various tobaccos on intradermal tests. Forty-four per cent of the 95 cases showed reagins or antibodies to tobacco. Since only 10 to 12 per cent of the positively reacting patients gave histories of allergy and showed reactions to ragweed or timothy, it may be assumed that only this number belonged to the atopic category while the remaining 68 per cent of cases with thrombo-angiitis obliterans became sensitized to tobacco as a result of excessive smoking. The development of tobacco reagins in this group indicated that they behaved in a manner similar to the atopic individual. In this respect, therefore, they may be compared with the asthmatic patient with a negative allergic background. That repeated exposure to tobacco may be followed by sensitization was proved by us in white rats who developed gangrene of the toes (11) simulating thrombo-angiitis obliterans as a result of repeated intraperitoneal injection of denicotinized tobacco. The animals thus affected were shown to be hypersensitive to tobacco by the Schultz-Dale reaction. That tobacco sensitization may, however, be more intense and involve characteristically more than one shock tissue in the atopic individual as compared with the so-called sensitized normal, is evident in the following case.

Case 2. History (Adm. 41-4750). P. F., aged 33, who had been smoking for 15 years 20 to 30 cigarettes daily developed a phlebitis in the left leg in 1935. This subsided on bed rest. In 1938 there appeared numerous boils over his arms and neck which continued for nine months and gradually subsided as a result of various forms of therapy. Early in 1940 he complained of pain in the ankles and both feet which persisted for about ten months. He was told he had arthritis, but x-ray examination failed to confirm this. Rest in bed for six weeks in addition to baking, brought about improvement in his condition. In December 1940 while still suffering pain in his feet he noticed an inflamed spot half way down his left leg. This was diagnosed as thrombo-phlebitis by his physician, Dr. Karson. On January 5, the phlebitis

increased in size. He returned to bed for a week with notable recession of the phlebitis under a regime of rest and wet dressings. On January 12, he experienced a vague sense of sticking pains and discomfort over his lower chest. In spite of this he got out of bed. In the evening of the following day he experienced a sharp pain in the left lower chest in the region of the spleen. This became severe and stabbing in character. There was a rise in temperature to 102°F. and chills. The patient was unable to take a deep breath or lie on the affected side. There was no cough or expectoration.

Examination. There was dullness over the left base of the lung posteriorly with absent breath sounds, fine moist râles and bronchophony. X-ray examination of the lung showed an area of infiltration in the left base accompanied by a small effusion. After 3 days in bed he developed pain over the right base of the lung. Examination disclosed some dullness and fine râles anteriorly and a friction rub posteriorly. A subsequent x-ray examination on February 2, 1941, showed a similar but smaller area of congestion at the right base together with a moderate amount of fluid. The heart was normal, the pulse was 100 per minute and blood pressure 139 systolic and 70 diastolic. The abdominal examination was negative. Half way down the right pretibial region there was a nodular area of phlebitis measuring $1\frac{1}{2} \times 2\frac{1}{2}$ cm.

Laboratory Data. The blood examination showed a leucocytosis varying between 17,200 and 10,400 with 88 to 84 per cent polymorphonuclear leucocytes. All other laboratory tests were negative.

Course. The course in the hospital was characterized by a rise in temperature which fluctuated between 102° and 103°F. On January 25 the temperature returned to normal. He remained in bed during the months of February and March. The lung signs and phlebitis improved progressively and at the time of his discharge there was no evidence of phlebitis. Immediately on leaving the hospital in March he resumed smoking from which he had refrained during the entire period of hospitalization. After several days he noticed the development of new phlebitic nodules, this time over both legs. They increased in number and became migrating in character. On the advice of his physician he went to the thrombo-angiitis clinic at The Mount Sinai Hospital on August 15. On examination the arteries of the right leg were normal, but on the left leg only the posterior tibial was patent while the pulses in the other vessels were closed. In addition, the phlebitic nodules noted above were also present over both legs. The diagnosis made by Dr. S. Silbert was early thrombo-angiitis obliterans associated with migrating phlebitis. An electrocardiogram taken at this time disclosed regular sinus rhythm, tendency to left axis deviation, small $Q_{1,2}$ and i , T_1 and T_4 low, T_2 diphasic and T_3 isoelectric. This suggested myocardial damage. Skin tests to tobacco showed an immediate positive one plus urticarial reaction to Burley and Maryland tobaccos. Two days later there appeared a delayed reaction, eczematous in nature at the site of the injected Virginia tobacco extract. In addition to these positive skin tests the patient showed two plus positive reactions to the pollens of *ragweed*, *timothy* and *plantain*. The presence of the latter without any history or symptoms referable to pollen sensitivity led to an investigation of his family background. This brought forth the information that one of his cousins, i.e. his mother's sister's son had ragweed hay fever and another, his father's brother's son, suffered with bronchial asthma. These facts together with the positive skin reactions to the pollen, obviously suggested an atopic heredity which was furthermore borne out by a personal history of pruritus, i.e. subclinical urticaria, since childhood. Other skin tests to foods and inhalants showed numerous positive reactions. He was told to stop smoking and to omit the positively reacting foods from his diet. He did this, with the result that the phlebitic nodules disappeared together with the generalized pruritus.

After the phlebitis had completely subsided he was retested to tobacco on August

29. Two days later he developed delayed reactions to Burley and Virginia tobacco together with new nodules of phlebitis over the left ankle. These remained until September 6, together with the delayed skin reaction to Virginia tobacco. With the disappearance of the latter the nodules also subsided. The question arose as to whether this short exacerbation of phlebitis was the result of absorption of the tobacco antigen from the skin test. To check this he was retested on September 10, after he had completely recovered from the previous reactions. This time he developed an immediate moderate urticarial response to Burley, Maryland and Nanthis tobaccos and a delayed reaction to Virginia tobacco which appeared within two days. The latter increased in size and intensity. It was about 3 cm. in diameter and also of eczematous character. Insidiously a new phlebotic nodule began to develop which reached its peak on September 23 and receded on September 25. Throughout this period the delayed reaction remained and when examined on September 26 it was still present, although the phlebotic area was practically gone. He also experienced headache, a sensation of fullness in the sinuses and pains in an area under the left knee, which had been a previous site of phlebitis, as well as "pimples" at the sites of his former boils. The patient volunteered the information that the phlebitis following the injection of tobacco extract was of shorter duration than that after smoking.

Comment. A constitutionally allergic patient with a history of pruritus since childhood and excessive smoking since adolescence, developed phlebitis in 1936, and generalized boils in 1938. In 1940 there was recurrence of the phlebitis followed by bilateral pulmonary symptoms which may have been an expression of migrating phlebitis of the pulmonary veins. In addition to these lesions evidence of thromboangiitis obliterans and myocardial involvement was disclosed electrocardiographically. The cause of these vascular manifestations was found to be tobacco, while that of pruritus was shown to be food allergy. Cessation of smoking and removal of the offending foods freed him of symptoms. It is possible that besides the constitutional factors the toxins of the bacteria responsible for the generalized boils which this patient had in 1938 had acted as an additional "preparatory factor" in the sense of Schwartzman and rendered his cardiovascular system much more vulnerable to the allergenic effect of tobacco than that seen in the usual non-atopic case of thromboangiitis obliterans in which the lesions are usually limited to one shock organ, namely the vessels of the extremities.

Polyvalent sensitization including tobacco, pollens and foods. Angina pectoris with coronary insufficiency, gastro-intestinal allergy.

In conjunction with our studies on thromboangiitis obliterans we found in testing 100 cases with coronary artery disease, that 44 per cent gave positive skin reactions. Passive transfer studies in 14 selected cases showed tobacco reagins in 71 per cent. This indicated a high incidence of antibody formation to tobacco usually characteristic of the atopic individual. The high percentage of atopy was furthermore supported by the finding that of the 100 patients investigated 33 per cent had a personal or family history of allergy in contrast to only 12 per cent of the patients with thromboangiitis obliterans and 25 per cent in a group of 400 normal control smokers in the general population. The high incidence of coronary disease in allergic individuals is significant of the extent to which the vascular system is involved in allergic reactions. This is illustrated in the following group of patients.

Case 3. History. J. D., aged 43, a physician, was first seen in 1939. He was subject to hives after exposure to cold water and also after hot showers or whenever he became overheated after exercise. He has had hay fever for many years, which usually started in May and continued for six weeks. His aunt also has hay fever. In 1936 he had an attack of arthritis involving both knees and elbows of about one year's duration. He had been smoking since the age of 16. For the past ten years he had been smoking about 40 cigarettes a day.

On April 1st, 1938 while seated on his porch and smoking, he suddenly experienced a severe attack of angina pectoris. This radiated to the epigastrium and continued for about 4 minutes. During the succeeding week, on April 3 and 5 he had similar attacks of anginal pain with radiation down both arms and upper abdomen for 3 to 4 minutes at a time. Following the third attack he noticed that his pulse was rapid and irregular for about one hour, gradually slowing down. He became alarmed and consulted a cardiologist. Electrocardiograms taken on April 6 showed inversion of T₁ and T₄, semi-inversion of T₂, suggestive of anterior wall infarction. He was told to stop smoking and rest. He refrained from the use of tobacco with distinct improvement in his precordial pain, but kept on working. On April 10, a second electrocardiogram was made and showed a return to normal. He tried smoking again, following which he immediately experienced a severe anginal seizure sufficiently convincing to cause him to stop smoking completely.

When seen in March 1939 he complained of a good deal of gastro-intestinal distress characterized by belching, distention and pyrosis as well as general intoxication and tachycardia after eating various foods. These symptoms were relieved to a certain extent by colonic irrigations. X-ray examination of his gall-bladder and gastro-intestinal tract was completely negative. He still had some precordial distress on exertion. Investigation from the allergic point of view indicated he was sensitive to numerous foods, inhalants, pollens and tobacco. A diet omitting the incriminating foods, removal of the offending inhalants and immunization to the grasses, which were responsible for his hay fever, brought about complete relief of his nasal symptoms, disappearance of the gastro-intestinal symptoms as well as the tachycardia. The only remaining symptom was slight precordial distress after exertion and eating. A re-examination of his diet disclosed that he was allowed to eat wheat and coffee to which he showed slight reactions. These were omitted and the distress after eating and on exertion disappeared. For the past two years while under observation he has been free of all untoward disturbances.

Comment. A 43 year old male with an allergic family background was first seen in 1939. He had an episode of angina pectoris with electrocardiographic evidence of coronary insufficiency in 1938, as well as various gastro-intestinal symptoms and tachycardia. Study disclosed that these various shock tissues were influenced by sensitivity to various foods, pollens and inhalants including tobacco. There was a striking affinity between these various allergens and the specific shock organs. With the omission of smoking the cardiac manifestations of angina terminated. Exclusion of offending foods led to the disappearance of the gastro-intestinal symptoms and of the few remaining possibly "reflex" cardiac manifestations. Immunization with pollen prevented a recurrence of his hay fever.

Bacterial allergy. Bronchial asthma with pulmonary infiltrations due to vascular allergy.

Case 4. History (Adm. 428216). F. H., female, aged 21, who had recurrent attacks of asthma since September 1934, was admitted to the hospital in August 1938 in status asthmaticus. In spite of seasonal variations in her attacks corresponding to the pollinating periods, skin tests with pollen etc. were found to be repeatedly nega-

tive. Associated with the paroxysms were repeated migratory interstitial pulmonary infiltrations, sputum eosinophilia, marked polyneucleosis and blood eosinophilia up to 54 per cent. With each acute asthmatic episode there appeared electrocardiographic changes indicative of abnormalities in the deflections and amplitudes of the P and T waves as well as the QRS complexes, suggestive of myocardial involvement. These, however, proved to be reversible in character returning to normal with the cessation of the asthmatic paroxysm. In the course of one of these attacks an acute pericarditis with constrictive phenomena supervened. While these were in progress the asthma subsided. With the termination of the cardiovascular symptoms which were present for almost a month, the patient developed an attack of polyarthritis lasting about a week. Following this there was an exacerbation of her asthma which slowly yielded to symptomatic therapy. She was discharged improved December 24, 1938, and readmitted in April 1939. On this occasion there was a return of the pulmonary infiltration previously noted, and in addition enlargement of corresponding hilar and paratracheal lymph nodes as well as right sided pleural exudate. There was again evidence of abnormal electrocardiographic changes in the P waves, QRS complexes as well as T waves in all leads. X-ray examination of the sinuses at this time still showed a bilateral antritis and ethmoiditis, especially on the right, and also involvement of the sphenoid sinus. As previously observed, with the disappearance of this attack the pulmonary as well as the electrocardiographic changes returned to normal.

In addition to sinus washings and autogenous vaccine injections she received short-wave treatment to her chest as well as hyperthermia. The latter aggravated the asthma as well as the temperature causing it to rise to 103°F. Whether this was symptomatic of physical allergy was a question. She responded to adrenalin by iontophoresis, and adrenalin in oil. She was discharged, only to return after several months with a recurrent attack.

On her seventh admission in April 1940 a bilateral Caldwell-Luc operation was performed because of the marked purulent sinusitis. She had a stormy recovery and finally left the hospital improved. She was readmitted for the eighth time in September 1940 with another attack of asthma. Thick pus was found in the ethmoids and sphenoids. Because of an extensive purulent nasal discharge, the elevation of the temperature to 104°F., and the presence of signs of meningeal irritation a sphenoidotomy was done. Shortly thereafter she developed an apurid pulmonary abscess. During this period the asthma disappeared. Sulfathiazole was administered and after three weeks the lung abscess gradually cleared up. She was well for several months until she entered the Montefiore Hospital in April 1941 because of the development of arthritis associated with recurrent reddish papular and urticarial skin eruptions. Biopsy of one of the papular nodules disclosed perivascular infiltrations with eosinophiles. The electrocardiogram which had returned to normal after her discharge from The Mount Sinai Hospital in 1940 was still unchanged except for tachycardia. She left the Montefiore Hospital in July 1941 slightly improved only to reenter The Mount Sinai Hospital on September 5, 1941 because of the return of the joint pains.

Examination. The arthralgias were migratory in character involving the hands, wrists, elbows, ankles and knees, associated with periarticular swellings which had a mottled pinkish appearance. The palm of the left hand which was enlarged and puffy was studded with reddish painful subcutaneous nodules. The skin over the extremities, back, umbilicus and genitalia showed numerous maculopapules on an erythematous base. There were also many pea-sized dark red, hard, tender and slightly hemorrhagic papules on the dorsum of both hands and along the bones of the forearm, associated with diffuse scaling and excoriations on the back of the elbows accompanied by psoriasiform patches. The temperature fluctuated between

101° and 103° F. The white blood cell count ranged between 15,100 and 9,000 per cm. with eosinophiles between 30 and 22 per cent. The lungs were clear and no cardiac abnormalities were detected on auscultation. The electrocardiogram, however, taken on September 9, 1941 showed low T_2 and T_3 and inverted T_4 . The latter had been upright on her previous admission. Biopsy of one of the papules, which unfortunately was not sufficiently extensive, showed subcutaneous fat tissue with diffuse acute inflammation and eosinophilia near the resected edge.

Course. Within a period of two weeks the arthritis gradually improved, the temperature receded and the patient was discharged. The electrocardiograph taken September 24, 1941 on the day of her departure showed T_2 and T_4 returning to normal.

Comment. A young woman of 21 with a negative family history for allergy had recurrent attacks of asthma for about seven years. The severe attacks were associated with pulmonary infiltrations, pleural effusions, pericarditis, polyarthritis, skin eruptions, subcutaneous nodules and marked eosinophilia. While the electrocardiographic changes appeared concurrently with the asthmatic attacks and returned to normal with their cessation they were in all probability not dependent on the respiratory anoxemia, but represented a phase in a generalized vascular reaction evident in the pericarditis and suggested in the biopsy of the papular urticaria which showed perivascular infiltration with eosinophilia. Further proof of this independence of respiratory anoxemia lay in the fact that on her last admission, electrocardiographic changes similar to those which accompanied her asthmatic seizures appeared in conjunction with the attack of polyarthritis and these likewise returned to normal with the termination of the arthritis. The arthritis too was of a peculiar character in that the swellings were periarticular, suggestive of an edema due to disturbed vascular permeability rather than to involvement of a joint. This was substantiated by x-ray examinations which failed to show any abnormalities in the bony structures.

The exciting factor responsible in the precipitation of these various manifestations, as far as could be determined, was bacterial allergy derived from the chronically infected sinuses from which this patient suffered for many years. In spite of repeated operative procedures on her sinuses the focus of infection had not been completely eradicated. Thus the exacerbations of symptoms in her numerous shock organs such as the lungs, cardiovascular system, skin and bone marrow, could be attributed to the continuous absorption of foreign proteins and toxins from her diseased sinuses, which flared up with each recurrent upper respiratory infection. In a series of cases of bronchial asthma recently reported by the writer entitled "Vascular Allergy," in which the major features presented by this case, which incidentally was one of that group, were practically identical, attacks of asthma in two of the patients as well as generalized purpura in one of these two, were precipitated by the injection of a minute quantity of vaccine of bacteria recovered from the washings of the infected sinuses. This indicated not only that bacterial allergy was responsible for the asthmatic reaction, but also that the capillary vessels were highly sensitized. The marked blood eosinophilia present in this case also testified to the allergic nature of the vascular manifestations. The shift from one shock tissue to another seen in the variety of alternating symptoms presented by her throughout her illness is also characteristic of allergic diseases as well as reminiscent of the protean manifestations of periarteritis nodosa. The difference between the simple allergic reaction and periarteritis nodosa is probably dependent upon the intensity of the vascular response. Whereas the histological appearance of the lesion in the skin resulting from the injection of a single allergen such as ragweed, is characterized by edema and perivascular infiltrations with eosinophiles, in periarteritis nodosa the reaction in the early stages may be similar but becomes more intense and progresses to actual productive inflammation of the vessel walls. That such a reaction may be

attributed to superimposed and repeated polyvalent sensitization by various agents in which in all probability viruses, bacteria, inhalants and foods as well as the inherent hyperergic state of the tissues play complimentary roles, has been pointed out by the writer in the previous publication quoted above. In two of the patients contained in that report who suffered from asthma and recurrent pulmonary infiltrations similar to those seen in the case under discussion, the transition between the simple allergic vascular response through the stage of eosinophilic arteritis, and periarteritis nodosa was clearly illustrated. In one of these patients, aged 11, microscopic sections of the lung disclosed eosinophilic arteritis of the pulmonary vessels and infiltrations of the interalveolar septums with eosinophiles, lymphocytes and polymorphonuclear leucocytes as well as fibrosis. The rest of the organs showed widespread periarteritis nodosa. The exciting factors responsible for the clinical manifestations in this case proved to be in the nature of polyvalent sensitization by pollens, foods, inhalants and bacteria. In the other patient, aged 38, in whom repeated sinus infection proved to be the major cause, the lungs disclosed thickening of the small vessels. Whether this represented the remains of allergic inflammatory reaction which did not progress to periarteritis nodosa such as was found in the vessels of the heart and liver of this case is a matter for conjecture. Microscopic sections of a biopsy specimen of a subcutaneous nodule removed from this patient during life, showed in some areas perivascular infiltrations with eosinophiles similar to those found in the urticarial lesions of the case herewith reported, while in other fields typical periarteritis nodosa was shown.

DISCUSSION

The four cases in this report represent allergic individuals who developed vascular disturbances involving capillaries, veins and arteries. These manifest themselves as purpura, in the first case, migrating phlebitis and thrombo-angiitis obliterans with myocardial involvement in the second; coronary artery insufficiency in the third; coronary artery involvement associated with bronchial asthma and recurrent pulmonary infiltrations in the fourth. The lesions were reversible in character as evidenced by the fact that following removal of the offending agent there was a disappearance of the presenting symptoms and a restoration to the normal of the tissues involved, with the exception of those that had been permanently damaged prior to observation.

The exciting agents responsible for the purpura in the first patient was found to be aspirin used for the relief of pain due to the tabetic crises. The period of 23 years required for the development of sensitization to the drug in question may be ascribed to two facts: first, the patient was non-atopic and consequently was sensitized with greater difficulty than an atopic, and second to the poor antigenicity of the drug. The involvement of the capillaries in this reaction was demonstrated by the positive tourniquet test indicative of capillary fragility. Since it is rather uncommon to see purpura due to ingestion of aspirin, although salicylates as such have been seen to produce purpura, the question may be raised whether this effect is merely the result of aspirin sensitization alone, the synergistic effect of the syphilitic infection plus aspirin, or whether the toxins of the spirochaetae, in the sense of Schwartzman, "prepared" the capillaries to the

sensitizing effect of aspirin. The latter would imply the creation of a shock organ where none existed. The answer to this last question may be ultimately found if the patient develops vascular syphilis at some future date.

In contrast to this case is the second, an atopic individual in whom hereditary influences probably played a significant role in the development of the numerous shock organs. The shock tissue affected consisted of the cardiovascular system, involvement of which was localized to the extremities comprising both arteries and veins, the lungs and myocardium. Whether the toxins of bacteria responsible for the generalized boils which this patient had in 1938, served as an additional "preparatory" factor and rendered the cardiovascular system much more vulnerable to the allergenic effect of tobacco cannot be excluded.

Polyvalent sensitivity characteristic of the constitutionally allergic person was indicated by the numerous positive skin reactions to foods, inhalants, pollens and tobacco which this patient presented. That tobacco was incriminated in the development of the vascular manifestations was proven by the arrest in the symptoms following its withdrawal and by the elicitation of phlebitic involvement on two different occasions following injection of tobacco extract intradermally. Such a sequence of events is uncommon unless the patient is highly sensitive to tobacco. A similar response was noted in one other patient with thrombo-angiitis obliterans after repeated administration of tobacco extract subcutaneously. This patient, free of all manifestations for two years, developed a generalized eczematous reaction associated with symptoms of thrombo-angiitis obliterans after the fifteenth injection.

In the third patient also an atopic individual the characteristic polyvalent sensitization and multiple shock tissues were again evident. The former was apparent in the multiple skin reactions to foods, inhalants, pollens and tobacco, the latter in the symptoms referable to the nose, gastro-intestinal and cardiovascular system. In the light of our thesis that the vascular system is probably the basic shock tissues implicated in the allergic response, these various manifestations indicate active sensitization of the vessels supplying the respective structures, rather than isolated organ involvement. The relative affinity between tobacco and the cardiovascular system is again illustrated in this patient by the disappearance of the angina pectoris and electrocardiographic deviations following the suspension of smoking. The amelioration of the residual precordial discomfort as a result of omission of wheat and potatoes is also significant. While distention of the stomach which this patient experienced after eating these foods may have contributed in a mechanical way to the precordial distress, such a distention does not occur in normal non-sensitive individuals, unless they are sensitive to wheat or potatoes. Although the question as to whether the wheat or potatoes were responsible for the precordial symptoms through their direct effect upon the vessels of the heart

or indirectly by way of distention of the stomach, or both, cannot be proven, the indication for the removal of the offending protein presents no controversial issue.

The fourth and last case serves as an illustration of a patient with asthma in whom the existence of atopy could not be established, yet the presenting symptoms and the marked eosinophile count left little doubt as to the allergic nature of the disease. Bacterial products arising from the sinus infection were probably responsible for the state of hypersensitiveness. Polyvalent or synergistic sensitization in this instance was attributed to recurrent upper respiratory infections caused by a variety of micro-organisms probably including viruses, throughout the seven years or more of her illness. These superimposed infections increased her hyperergic state because of her inability to achieve immunity. They were also responsible for the creation of the multiple shock organs in contrast to the atopic individual in whom hereditary influences play the determining role. The mechanism involved in the development of these shock tissues was probably similar to that operative in the Schwartzman phenomenon in which bacterial toxins "prepare" the vessels for subsequent attack by endogenous or exogenous bacterial infection. While the disease manifestations were apparently localized in different organs, the underlying participation of the vascular system was clearly evident in the pericarditis and pleuritis which, according to Eppinger represent disease of the capillaries of the serous membranes, the electrocardiographic changes, the periarticular swelling and the papular urticaria which showed perivascular eosinophilic infiltrations.

The repeated exacerbations of this vascular syndrome followed by recovery of the patient during the past seven years, indicates that bacterial allergy similar to allergy to non-living proteins may also be reversible, depending upon individual resistance. In some of the cases reported by me (12) and one recently observed, having symptoms identical with those presented by this case, the hyperergic vascular reaction became irreversible within a period of two to three years progressing to periarteritis nodosa seriously involving the heart in one instance and the kidneys in another, followed by a rapid exitus. Whether the hyperergic process in this case will become arrested or progressive will be the subject of a future report.

SUMMARY

1. Four cases presenting cardiovascular involvement in which capillaries, veins and arteries participated, are reported.
2. Constitutional allergy or atopy were present in three of the four patients.
3. The exciting agents proved to be drugs, tobacco, pollen, foods and bacteria.

The various manifestations are regarded as the expression of vascular allergy.

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THE EFFECT OF ROENTGEN THERAPY IN PRIMARY CANCER OF THE BREAST

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Sporadic attempts have been made for many years to treat primary cancer of the breast by roentgen therapy. It is only recently, since the better definition of cancericidal dosage and since the introduction of the principle of protracted fractionization of the therapy (Coutard), that more serious efforts have been made to ascertain the value of preoperative radiation therapy in this disease. Statistical data on large numbers of patients with breast cancer treated by surgery alone or with postoperative radiation therapy are now available. It is obvious that the results are not satisfactory. In studying end results from surgery the fact is often overlooked that the reports include only operable cases, which constitute about 50 to 60 per cent of the material in general hospital practice (Keynes (1), Wintz (2)). Review of 124 consecutive patients from two of the author's clinics, from 1935 to 1938, showed a 42 per cent operability rate (Table I).

EVALUATION OF MATERIAL

Operability is determined by the anatomical extent of the disease or by the presence or absence of complicating organic disease or by both. The terms "clinically operable," "technically operable," and "inoperable," used by Heyman (3) in his study of corpus carcinoma, may be employed to good advantage in classifying breast cancer. "Clinically operable" refers to patients with operable tumors and no organic contraindication to radical surgery. "Technically operable" refers to patients with operable tumors in whom surgery would be dangerous on account of complicating organic disease. "Inoperable" refers to patients with disease too extensive for complete removal, or with remote metastases beyond the axilla (Table I). Although mortality following the so-called radical operation for cancer of the breast is low, in many instances organic disease, especially in the aged, causes death much sooner than the slow-growing tumors so often found in these patients. In this latter group, no treatment, or only conservative treatment, is indicated.

There is still a lack of unanimity as to what is meant by operability among surgeons. Harrington (4), for instance, includes patients with encuirasse nodules, or unilateral supraclavicular nodes, as operable; patients with distant metastases are also occasionally operated. In general, however, the presence of such deposits is considered a sign of incurability

and radical surgery is not performed. In fact, many surgeons consider bulky tumors, wide skin adherence, inflammatory cancer, cancer in the pregnant and the presence of large fixed axillary nodes as clinical signs of incurability even when grossly removable. A distinction must be made between surgically operable and surgically curable. Such variations in the criteria for operability, the lack of statistics for absolute five-year cure rates, where the entire material was not considered, and controversial pathological diagnoses, all tended to give one a distorted picture of the results of surgery for cancer of the breast. This was especially true of the literature up to ten years ago. The problem in recent years has been complicated in many instances by the addition of postoperative or so-called prophylactic radiation therapy.

There is a uniformity of opinion regarding the better prognosis and curability by surgery where the axillary nodes are not involved. This favorable group constitutes about 32 per cent of the operable cases and about

TABLE I
Operability of 124 consecutive mammary cancers

	NUMBER	PER CENT
1. Clinically operable.....	51	42
2. Technically operable*.....	16	13
3. Inoperable.....	57	45
	124	100

* Complicated by severe organic disease.

Note: 68 of the above patients are from the Tumor Clinic, Morrisania Hospital, Bronx, New York.

20 per cent of the entire material. The five-year cure rate from radical mastectomy in this group is 70 per cent. Eighty per cent of the patients, when all cases are included, have axillary involvement, and if the radical operation is performed on the operable patients in this group, most of the reports record a 20 per cent five-year survival.

The surgical technique for radical mastectomy introduced by Halsted and Meyer for the radical removal of the breast and the axillary contents has not materially improved since its inception. Lacking a specific cure for cancer, it would seem natural to look for improvement in our results by the use of other methods. No one will deny that earlier operations before there is extension to the axillary nodes offer a fruitful field for improvement. Some benefit will be derived undoubtedly from the anti-cancer campaigns which are doing such splendid work along these lines. However, the layman's procrastination, modesty and fear of the possibility of cancer, and occasionally the physician's attitude of watchful waiting or misguided dismissal of lumps in the breast, have been an obstacle to early

diagnosis and successful treatment. The removal and examination of every suspicious breast lump is still the best teaching for general use and, if practised universally, would definitely improve our results.

Dissatisfaction with radical mastectomy for operable cancer of the breast has been expressed by many surgeons, including Keynes, Souttar (5), Fitzwilliams (6), Wintz, etc. Others, including the late Drs. Lee (7) and Bloodgood (8), and recently Adair (9), have used preoperative irradiation, while some advised simple mastectomy with irradiation of the axillary contents (Grace (10)). Similarly, certain members of the surgical staff of The Mount Sinai Hospital expressed dissatisfaction with the results

TABLE II
Physical factors

K. V.	FILTER	DISTANCE	SIZE OF PORTAL
180-200	0.5 mm. Cu 2.0 mm. Al (occasionally Thoreus)	50 cm.	6 x 8 to 10 x 15
Portals	4-5" overlapping	BREAST	AXILLA
		Direct Upper Lower Mesial Lateral	Anterior Direct Posterior
Dose per port	1200r 1600r 4000r 6000r	5 ports 4 ports Single Ports	2000r
Daily dose	300-450r	Divided between 3 areas	
Treatment time	30-40 days	30-40 days	

"r," international, measured in air.

from surgery and agreed to study the effects of preoperative roentgen therapy.

This study was carried out for a period of five years (between 1935 and 1940) on 75 cases of operable cancer of the female breast with the aim of determining the effect of intensive fractionated roentgen therapy on the primary tumor in the breast and the axillary lymph nodes. All cases in this group showed definite clinical evidence of cancer in the breast and positive aspiration biopsies. Roentgen therapy was directed mainly to the breast and axillary contents; no attempt was made to irradiate the thoracic cage, in fact great care was exercised by the use of tangential irradiation to avoid exposure to the pleura and lungs. The physical factors used in the

roentgen therapy are shown in Table II. The estimated tissue dose to the primary tumor in the breast varied from 4,000 "r" to 7,000 "r"; the minimum tissue dose to the axilla was 2,600 "r".

CLINICAL CONSIDERATIONS

The usual roentgen dermatitis occurred about three weeks after onset of treatment and healed about two to three weeks after completion of therapy. Shrinkage of the primary tumor occurred in over 60 per cent of the patients, in some going on to complete clinical disappearance. However, in most of these cases regrowth was apparent usually four to six months later, thus indicating only partial sterilization of tumor or temporary restraint of growth. The axillary nodes failed to show similar striking diminution in size. There were regressive changes in about 50 per cent of the cases; most of these were probably inflammatory. The presence of cancer in the axillary nodes was proven only in a small percentage of the more advanced cases with large deposits. The interval between completion of radiation therapy and mastectomy varied considerably. The minimum interval was

TABLE III

Pathological findings in seventy-five irradiated cancers of the breast followed by mastectomy

	NUMBER	PER CENT
No cancer in breast and axilla.....	9	12.7
No cancer in breast, axilla positive.....	1	1.3
Cancer in breast, axilla negative.....	18	24
Cancer found in breast and axilla.....	47	62

six weeks, the maximum two years. The longer interval occurred in cases of borderline curability, or where ulceration was considered imminent.

Radical mastectomy was performed in all but four instances. In the latter simple mastectomies and axillary biopsies were done. Satisfactory healing following mastectomy occurred in most cases. This was due to the fact that the irradiation was planned so as not to cross-fire the lines of incision. There were no cases of pleuro-pulmonitis.

PATHOLOGICAL FINDINGS

The gross appearance of some of the excised breasts, especially the sterilized ones, failed to show marked changes; others showed gross fibrosis and distortion, especially if the interval between radiotherapy and surgery had been of long duration. Microscopic examination revealed hyalinization, calcification and marked fibrosis in some of the breasts and, to a lesser degree, in the axillary lymph nodes. The site of the center of the original tumor showed these radiation changes most strikingly. In many cases only peripheral islands of a few cancer cells could be found. In evaluating

these findings, the presence of any cancer cells, regardless of number or arrangement, was considered an unsterilized case. No attempt at grading radiation changes was made. Cases reported as suspicious of cancer were also classified as failures to eradicate the disease. We know of no accurate method at present of distinguishing between viable and non-viable cancer cells as found in these sections. The pathological findings in the cases studied are shown in Table III.¹

COMMENT

The sterilization of only 13 per cent of the breast tumors challenges the advocates for the use of roentgen therapy as the only form of treatment for operable breast cancer. Roentgen therapy as it is administered today cannot compete even with simple mastectomy where at least all of the primary tumor can be removed.

The finding of 63 per cent involved lymph nodes indicates our inability to sterilize axillary deposits. Some superficial nodes showed peripheral segmental scars, indicating that cancer had been present but had been destroyed. Deeper lymph nodes and in some cases adjacent ones, showed cancer. The odd shape of the axilla presents certain technical problems which may be overcome by newer radiological methods. Proponents for the questionable idea that it is safer to remove the more quiescent irradiated tumor must balance this point of view with the real mortal danger of delay that a program of preoperative roentgen therapy necessitates.

Patients seldom die because of the presence of a tumor in the breast. Metastatic deposits kill the patient. To combat this our best plan for the present is immediate radical mastectomy in properly chosen cases.

There is ample clinical and pathological evidence that radiation therapy causes growth restraint in primary cancer of the breast. A small percentage of breast cancers can be sterilized by radiation therapy but this cannot be favorably compared with the results of radical mastectomy in operable cancer of the breast. The indications for the use of roentgen therapy, therefore, limit themselves to the inoperable cases, to those showing metastases beyond the axilla, and as a so-called "prophylactic postoperative" agent. Inflammatory cancer and cancer in pregnant patients have been shown to do badly with surgery. Radiation therapy will not cure these patients but the palliative effect is greater and the mutilation of surgery is avoided.

CONCLUSIONS

Seventy-five patients with proven cancer of the breast received intensive preoperative roentgen therapy.

Pathological studies after mastectomy showed 13 per cent sterilization

¹ A more detailed report on these findings, correlated with the actual dosage delivered to the tumor, will be published later.

of the primary tumor in the breast. The finding of 63 per cent involved axillary nodes in operable material indicates that no cancerolytic action occurred in these deposits. In view of these findings radical mastectomy should be recommended as the treatment of choice in operable cancer of the breast without the delay and questionable benefit of preoperative roentgen therapy.

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CLINICAL SYNDROMES PRODUCED BY TEMPORARY DISTURBANCES OF THE CEREBRAL CIRCULATION

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Since Dr. Oppenheimer has long been recognized as one of the leaders in the development of our modern concepts of cerebral vascular disorders, it is a pleasure to write for his Anniversary Volume an article dealing with a subject of particular interest to him.

There are several disorders in which at one time or another the patient suffers from a temporary disparity of oxygen to the brain. Since knowledge about the causation of these syndromes is still decidedly incomplete it is in order that these conditions be approached with humility rather than with dogmatism. The discussion to follow must, therefore, be regarded as representing a tentative point of view which will need to be modified as further and more accurate information becomes available. Due recognition must be given to the fact that the physiological approach to these syndromes is intended not to supplant but only to complete the more usual etiologic and pathologic viewpoint. The generic phrase "cerebral vascular episode" used to embrace the entire group of disorders, and the other terms applied to the several different syndromes are purely descriptive. They are used as a matter of convenience rather than on the basis of any structural change in the body.

Regardless of the underlying disease process the cerebral vascular episode lasts for minutes, hours, or at most for a day or two. Hence, it needs to be sharply differentiated from the cerebral vascular accident (due to hemorrhage, thrombosis or embolism) in which the symptoms are of longer duration. Since almost any part of the central nervous system may suffer for one reason or another from a sudden diminution in blood supply, it is not surprising that very variable and at times puzzling features may occur. One can often differentiate the syndromes observed into two groups, according to whether the manifestations are mainly *general*, i.e., dependent on a diminution in the blood supply to all parts of the brain, or predominantly *focal*, i.e., referable to a circulatory disturbance in some part of the brain. The important features of the first group are weakness, apathy, stupor, unconsciousness, generalized convulsions and delirium. Among the very variable focal phenomena which may occur are disturbed motor function, as manifested by paralysis, convulsions or aphasia; disorders of somatic sensation, as numbness, tingling and other parathesias; and dis-

turbances of the special senses, especially of vision and hearing. The attacks are commonly accompanied by alterations in blood pressure, disorders of respiration, changes in the pulse rate, and less frequently by abnormalities of the rhythm of the heart. The important point as regards differential diagnosis is that the disturbance is sudden and of relatively short duration, lasting at most a day or two, and frequently for a much shorter time.

Cerebral vascular episodes occur in diverse diseases and may be brought about by several different fundamental mechanisms. A classification based on the type of underlying physiological disturbance is shown in Table 1. This tabulation is not intended to be all-inclusive but embraces only those disorders with which I am familiar from personal experience. Doubtlessly there are other syndromes which fall into this general group. In the following discussion emphasis will be placed chiefly on those syndromes which are most frequently misunderstood and incorrectly diagnosed.

1) *Decrease in blood supply to the brain associated with a general diminution in circulation to the body tissues in general. (Acute circulatory failure.)* In this group are included all the conditions which may produce the syndrome of circulatory collapse. These may be:

(a) *Hematogenic*: as the result of a decline in blood volume brought about by internal or external hemorrhage, by trauma, by dehydration from vomiting, diarrhea, excessive sweating or burns.

(b) *Neurogenic*: as in simple fainting, carotid sinus syncope, or due to the induction of spinal anesthesia; or

(c) *Cardiogenic*: as the result of either sudden extreme changes in the heart rate, or of acute damage to the cardiac musculature.

The subjects with acute circulatory failure exhibit the manifestations of circulatory collapse, i.e., ashen pallor, clammy skin, marked tachycardia (or more rarely, bradycardia) and usually a decline in the blood pressure, particularly in the pulse pressure. In the hemorrhagic and neurogenic types the veins are empty; in the cardiogenic type they are apt to be over-distended. The cerebral manifestations consist only of apathy in the milder cases but in severer instances stupor, coma or delirium may be observed. Focal manifestations are usually absent in the cases which fall into this general group.

Special mention may be made of carotid sinus syncope, a syndrome once regarded as rare but now recognized as relatively common. Weiss and Baker (1) pointed out in their original description of this symptom-complex that it consists of attacks of faintness or actual syncope, with or without convulsions as the result of hypersensibility of the terminals of the carotid sinus nerve (Hering's nerve), which arises in the carotid artery just proximal to its bifurcation, joins the glossopharyngeal nerve and, passing to the brain stem, exercises a powerful reflex effect on the medullary

TABLE I
Cerebral vascular episodes

MAIN GROUPS	GENERAL SYMPTOMS	SUB GROUPS	SYMPTOMS	CHIEF UNDERLYING PHYSIOLOGICAL DISTURBANCES	EXAMPLES	SPECIAL SYMPTOMS	CEREBRAL SYMPTOMS
I. Sudden decrease in blood supply to tissues, including brain (acute circulatory failure)	Collapse; weakness; faintness; clammy skin; lowering of blood pressure; changes in heart rate	Hematogenic	Secondary shock	Decrease in blood volume	Hemorrhage, dehydration	Venous empty	<i>General:</i> Apathy, stupor, unconsciousness, convulsions.
		Neurogenic	Primary shock	Vasodilatation	Simple fainting, carotid sinus syncope, spinal anaesthesia		
		Cardiogenic	Acute cardiac failure	Diminution in cardiac output	Coronary thrombosis, pericardial effusion, paroxysmal tachycardia, Adams-Stokes disease	Venous distended, rales at lung bases	
II. Sudden decrease in blood supply to brain only (hypertensive encephalopathy)	Hypertension	Acute relative hypotension		Sudden decline in elevated blood pressure in patients with cerebral arteriosclerosis	Over dosage with vasodilator drugs	Blood pressure below normal level	Stupor; rarely focal symptoms
		Acute pseudo-uremia	Renal convulsive disorder	Cerebral vasospasm and/or cerebral edema	Eclampsia, acute nephritis	Increased intracranial blood pressure, above usual level	
		Cerebral vascular crisis	Chronic pseudo-uremia, pseudo-apoplexy	Cerebral vasospasm	Sudden hemiplegia, clearing up in a few hours	Blood pressure above usual level	
III. Increase in metabolism of brain in proportion to its blood supply	Sudden increase in basal metabolic rate	Hypertensive myelopathy (rare)		Vasospasm in spinal cord	Temporary paraplegia	Blood pressure above usual level	<i>Focal:</i> Paraplegia, sensory changes in legs
		Without cerebral arteriosclerosis		Excessive increase in metabolism in young subjects	Thyrotoxic crisis, hyperpyrexia	Metabolism above patient's usual level	
		With cerebral arteriosclerosis		Moderate increase in metabolism in permanent cerebral arteriosclerosis	Thyroid therapy, moderate fever		

vegetative centers. The symptoms appear to be brought about either by vagal inhibition of the heart, by sudden marked lowering of the blood pressure, or less commonly, by reflex effects on the brain. In some of the reported cases tumors of the carotid body or enlarged cerebral lymph nodes have been responsible for these seizures. The attacks have sometimes been induced by changes of posture or by simply turning the head. This syndrome has been confused in the past with other conditions, particularly with idiopathic epilepsy. Its recognition is important because it can usually be helped by drugs and can sometimes be cured by denervation of the affected carotid sinus. The cardinal diagnostic feature is that the exact clinical picture which occurs in the spontaneous attacks can be induced at will by pressure on one or the other carotid sinus.

In patients with circulatory collapse due to any cause the type and extent of the cerebral manifestations depend on three factors: 1) the *suddenness* of the onset, other things being equal, the cerebral manifestations are more outspoken when the collapse is of sudden onset; 2) the *severity* of the collapse, and finally 3) on the *preexisting state of the cerebral vessels*. The latter point is of particular importance, for the patients with latent and asymptomatic arteriosclerosis of the brain may develop well marked cerebral symptoms with general circulatory disturbances which are so slight as to produce no manifestations in young persons free of cerebral arteriosclerosis.

In the treatment of the cerebral disturbances common to this group of disorders proper attention to the underlying disturbance is of prime importance. Thus, in the hematogenic type of collapse control of hemorrhage, if present, transfusion and the administration of fluids are indicated. Vasoconstrictor drugs may be of value in the neurogenic type. Atropine, epinephrine and ephedrine are helpful in certain patients with carotid sinus syncope. Collapse of cardiogenic origin is also frequently benefited by drugs such as digitalis (in paroxysmal auricular tachycardia), quinidine (in paroxysmal ventricular tachycardia), epinephrine and barium chloride (in the Adams-Stokes syndrome). Symptomatic therapy alone without a clear recognition of the nature of the disturbance responsible for the cerebral symptoms will usually end in failure.

2) *Decrease in blood supply to the brain only.* Persons suffering from hypertension are particularly predisposed to cerebral vascular episodes. Aside from the group of disorders mentioned above, which may occur in hypertensive as well as non-hypertensive subjects, there are three syndromes which appear almost exclusively in individuals with elevated blood pressure. One of these, which has been described and called "*acute relative hypotension*" by Stieglitz (2), is closely allied to the disturbances characterized by circulatory collapse. When for any reason a patient with elevated blood pressure and cerebral arteriosclerosis develops a sudden decline in blood pressure either from vasodilator drugs, from one of the

disorders already discussed, or for no apparent reason, the patient may exhibit the cerebral symptoms of hypotension even though the blood pressure is still above the normal level. Depending on the extent of the cerebral vascular disease the symptoms may be either of the general or of the focal type. A knowledge of the previous level of the blood pressure prior to the attack is of importance here in differentiating this condition from the "*cerebral vascular crisis*" [Pal (3)], which also occurs in persons with hypertension. In attacks of the latter type the blood pressure rises above its usual value and the patient experiences either general symptoms such as headache and prostration, or focal manifestations which may be of the most varied types. Transient monoplegias or hemiplegias, lasting only a few hours and often accompanied by loss of consciousness, as well as convulsions, parathesia, amaurosis, deafness or aphasia may occur. When seen shortly after the onset, patients with this condition are often erroneously considered as having apoplexy by the physician, whose pleasure at the rapid recovery is likely to be tempered by embarrassment at the inaccuracy of his prognostication. Since it is frequently impossible to differentiate these seizures from true apoplexy in the beginning it is wisest to withhold a positive opinion for a day or two in such instances.

Attacks of this nature, but involving the spinal cord rather than the brain, do not seem to have been described in the literature. I have recently seen a patient (case 4 below) who had attacks of paraplegia associated with a temporary rise in blood pressure which disappeared after a few minutes. Between the seizures neurological examination revealed no abnormalities. This condition might be termed *hypertensive myelopathy*.

The attacks of cerebral vascular crisis [also called "chronic pseudo-uremia" by Volhard (4), and by Becher (5)] are best prevented by sedative drugs, the barbiturates in repeated small doses being especially useful. Venesection sometimes promptly relieves an attack and also appears to be of prophylactic value. It is most important to treat the congestive heart failure which so often coexists. Drastic restriction of fluids to 700 cc. or less daily and of sodium chloride, as practiced in Volhard's clinic, is believed by Becher to be of great value. The same author urges the use of diuretics even in the absence of cardiac failure or of edema. Vasodilator drugs, particularly sodium nitrite, pilocarpin, papaverin and various xanthine derivatives have been recommended. When, as is not rarely the case, the seizures are accompanied by Cheyne-Stokes respiration, aminophylline intravenously may be of benefit.

Closely allied to the cerebral vascular crisis is the condition named by Volhard, "*acute pseudo-uremia*" ("*Nierenkrampfleiden*, "renal convulsive disorder"). This latter condition is called eclampsia when it occurs in pregnant women but an identical syndrome is observed in children and in some young adults with acute glomerular nephritis. It is less frequent in chronic glomerular nephritis and in the various types of essential hyper-

tension. All the patients with this symptom-complex have hypertension and many of them have edema. Evidences of renal damage are found in the urine but the disorder is entirely independent of renal insufficiency, for it usually occurs in the absence of nitrogen retention. (In the older descriptions this condition was confused with uremia from which it was clearly separated by Volhard.) The symptoms of this condition are predominantly those of increased intracranial pressure. In the less severe cases, headache, choked discs, vomiting and bradycardia may be observed. When the condition becomes more severe, generalized convulsions, usually accompanied by loss of consciousness set in. During and prior to the attack there is a rise in the already elevated blood pressure. A few of the patients exhibit temporary blindness, deafness or paralysis. The condition is likely to be confused with meningitis because of the cervical rigidity, increased reflexes and positive Kernig and Babinski signs, as well as the increase in body temperature which may occur. In the treatment of acute pseudo-uremia the therapeutic measures of greatest value are venesection, lumbar puncture, sedatives, magnesium sulphate [Blackfan and Hamilton (6)], intravenous hypertonic glucose and the management of congestive heart failure when this condition coexists. Becher states that much benefit is produced by complete withdrawal of food and restriction of fluids to the absolute minimum.

The foregoing paragraphs may seem to indicate that the cerebral vascular crisis and acute pseudo-uremia are entirely separate clinical entities. This is not the case and there is much justification for grouping them together under the term "*hypertensive encephalopathy*" as has been done by Oppenheimer and Fishberg (7). Since the two conditions shade into each other and often coexist they cannot always be sharply differentiated. However, the cerebral symptoms are usually general in the patients with acute pseudo-uremia who are ordinarily young and free of arteriosclerosis of the brain, while the symptoms of the cerebral vascular crisis are often focal, occur in persons with chronic hypertension and with some cerebral arteriosclerosis.¹ Furthermore, while it seems to be generally agreed that vasospasm is the cause of attacks of the latter type there is some dispute as to whether in the former condition the vasospasm is primary and the cerebral edema secondary, or whether edema of the brain (as result of capillary injury, contraction of the veins, or unknown mechanisms) is the

¹ It seems probable that this difference in the character of the symptoms is to be explained by the irregular distribution of the sclerotic process in the cerebral vessels of the older hypertensive patients. If some of the vessels are already narrowed as result of the disease but are still capable of contraction, it is probable that generalized cerebral vasoconstriction will affect the areas supplied by these particular vessels most and hence produce focal manifestations, while in the younger subjects with eclampsia or with acute nephritis and without arteriosclerosis, the cerebral vasoconstriction will affect all parts of the brain more or less equally and hence produce general rather than focal phenomena.

initial change with ischemia resulting from compression of the vessels within the rigid skull.

3) *Increased metabolism of the brain in proportion to its blood supply.* Thus far we have considered conditions in which the cerebral circulation is insufficient in the absolute sense. Physiologically an analogous disturbance may be produced if the demand for oxygen in the tissues of the nervous system be increased to a greater degree than the circulation to these tissues. An increase in volume flow through an organ can occur either as the result of the speeding up in the rate of movement of the blood through a constant vascular bed, as the result of an opening up of new channels, the velocity of flow remaining constant, or by a combination of these processes. In the brain the degree to which vascular dilatation can take place is sharply limited by the rigid cranial cavity. It is, therefore, not surprising that when the metabolism of the body is markedly increased either as the result of hyperpyrexia or of very excessive thyroid secretion the brain appears to suffer more than the other tissues. Here again the symptoms are usually general, consisting of stupor and delirium, rather than focal manifestations. The influence of excessive fever on the cerebral functions is so well known as to require no further comment. However, it does not appear to be sufficiently recognized that in a patient with cerebral arteriosclerosis identical symptoms may be produced by a relatively slight elevation of temperature. On several occasions I have observed elderly patients with recurrent stupor in the afternoon when the temperature was 102 to 103°F., with normal mental function during the morning when the temperature was at or near a normal level. The obvious explanation is that the diseased vessels were able to transport sufficient blood so long as the metabolic rate of the tissues was normal, but were unable to accommodate themselves to the increase in blood supply which was needed when the metabolism rose as the result of fever.

An analogous condition is occasionally observed when thyroid extract is administered to certain elderly patients with myxedema. Here as the manifestations of hypothyroidism improve the mental state of the patient deteriorates progressively, resulting in stuporous delirium which is relieved by withdrawal of thyroid medication and again induced and again relieved by the same measures.

The following case reports are illustrative of some of the less well known syndromes which have been mentioned.

CASE REPORTS

Case 1. History. G. D., aged 74, complained of attacks of faintness which were sometimes accompanied by unconsciousness. Examination was negative except for slight generalized arteriosclerosis and some cardiac enlargement. Attacks could be regularly induced by pressure over the left carotid sinus. Similar pressure over the right had no effect. Electrocardiograms were normal but complete heart block with ventricular standstill lasting five seconds was induced by pressure on the left carotid

sinus. Several months later the patient spontaneously developed two-to-one heart block. She has continued to have attacks for the past 18 months in spite of various drugs which have been employed.

Comment. In this patient seizures of the Adams-Stokes syndrome occurred spontaneously and could be induced by pressure over the hypersensitive left carotid sinus. The condition is apparently not very unusual for I have recently seen several similar cases.

Case 2. History. M. S., a 50 year old female, had marked hypertension (250 systolic and 150 diastolic), with manifestations of congestive heart failure and severe intermittent headaches. She awakened one night feeling numb and "dead all over" but without paralysis. These symptoms cleared up within thirty minutes. A month later she had an attack of sudden deafness in the right ear which lasted only a few minutes. She also had repeated attacks of unconsciousness with clonic convulsions lasting ten minutes or less. On three occasions she had sudden loss of vision which cleared up within an hour. In no instance were any lasting abnormal neurological signs observed after recovery from these several types of attacks. Some of the seizures mentioned occurred while the patient was under observation in the hospital and on each occasion the blood pressure was found to be above its usual level. She eventually died of renal insufficiency. Autopsy revealed advanced arteriosclerosis of the cerebral vessels with scattered punctate recent hemorrhages in the basal ganglia on both sides of the brain.

Comment. This patient presented the two cardinal features of the cerebral vascular crisis, i.e., temporary disturbance of the function of the brain and elevation of the blood pressure above its usual height during the attacks.

Case 3. History. E. H. a 22 year old primipara, noticed generalized edema during her fifth month of pregnancy. One morning during the eighth month she awoke suffering from a headache which became increasingly severe. The following morning she could not be aroused and had a generalized convulsion, which recurred the two following days. On examination she was stuporous, her face was puffy and there was slight pitting edema of the extremities. The blood pressure was 190 systolic and 160 diastolic. The retinal veins were full and the margins of the optic discs were indistinct. The heart was entirely negative to physical examination. The urine showed a large amount of albumin, specific gravity as high as 1.026, numerous hyaline and granular casts, no red cells or white cells. The blood uric acid was 8 mg. per cent, and the non-protein nitrogen was 33 mg. per cent. Lumbar puncture revealed a cerebrospinal fluid pressure of 320 mm. of water. Following cerebrospinal fluid drainage, the use of sedatives, and small amounts of hypertonic glucose intravenously, the blood pressure declined to 140 systolic and 110 diastolic. The convulsions ceased and she became rational. Several days later the heart rate suddenly increased to 160 with regular rhythm and the blood pressure diminished to 120 systolic and 104 diastolic. She became comatose, the pulse was feeble and the skin cold and wet. Electrocardiograms revealed auricular flutter with two-to-one auriculo-ventricular block. She was given a preparation of digitalis intravenously. This caused some slowing of the heart rate which became irregular. While a quinidine solution was being prepared for intravenous injection the patient died. Permission for autopsy was refused.

Comment. Here we have cerebral vascular episodes of two different types in the same patient. The combination of headache, choked discs, increased cerebrospinal fluid pressure, convulsions and stupor occurring in the latter months of pregnancy with urinary findings indicating renal damage, but with good ability to concentrate and without elevation of the non-protein nitrogen of the blood, represents a typical

picture of the eclamptic form of acute pseudo-uremia. The later development of auricular flutter led to the picture of acute relative hypotension, the collapse being of the cardiogenic type. The patient had all the symptoms of hypotension in spite of the normal systolic blood pressure and an elevated diastolic blood pressure.

Case 4. History. F. H., male, aged 63, had noted ringing in the ears for seven years, and increasing dyspnea on exertion for five years. Seven weeks before he was first seen he noticed while walking that his legs felt heavy and numb. A moment later they felt as if they were swollen and he was unable to tell where they were. He suddenly became unable to stand and fell to the floor. Improvement began within a half hour and recovery was complete within two hours. During the attack he was seen by his physician who told him that his blood pressure was "higher than usual." Two weeks later he had a similar attack during which he was told that his blood pressure was 210. After the attack had cleared up completely his blood pressure was 180. In neither seizure was there impairment of consciousness. The following week he had two attacks of diplopia, both of which lasted a few minutes and then cleared up completely.

At the time the patient was examined the neurological findings were negative, the blood pressure was 165 systolic and 90 diastolic, the heart was slightly enlarged, and there were a few râles at the bases and slight pitting edema of the lower extremities. The manifestations of cardiac failure cleared up quickly under digitalis therapy.

Comment. Although this patient was not seen during any of his seizures the history suggests that the attacks of diplopia were dependent on intracranial vasospasm. The sudden changes in motor and sensory functions with rapid recovery can best be accounted for by the assumption of vasospasm in the spinal cord (hypertensive myelopathy).

Case 5. History. E. E., a 69 year old man had, following suprapubic drainage of the bladder for a prostatic obstruction, pronounced pyuria with an irregular but slight elevation of temperature. Eight days after operation he developed a stuporous state associated with muttering delirium but without any signs of focal disease of the nervous system and with only minimal nitrogen retention in the blood. His temperature at this time was 103°F. The following morning the temperature was 99°F. and he was perfectly clear mentally. In the afternoon fever again developed (103.4°F.) with recurrence of stupor and delirium which disappeared again as the fever subsided.

Comment. This sequence of events is not uncommon in elderly subjects but is rarely observed in young adults except when the fever is much greater in degree. It seems probable that inability of the arteriosclerotic vessels to adjust themselves to the increased metabolic needs of the brain during febrile periods is responsible for this syndrome.

Case 6. History. V. S., a white female, aged 62, presented the classical evidence of outspoken myxedema, with a basal metabolic rate of minus 46 per cent. She also had substernal pain on effort, thickening and beading of the peripheral arteries and a blood pressure of 182 systolic and 112 diastolic. She was intelligent and showed no evidence of mental impairment other than slight lethargy and slowness of reaction time. These manifestations were attributed to the lowered metabolism. On September 24, she was started on 3 gr. of thyroid extract daily. Two days later she was much improved subjectively, felt less cold, noticed her skin was moist for the first time in years, her voice was higher pitched and her body temperature had risen from 97 to 98°F. Four days after starting thyroid medication improvement was still more definite and the basal metabolic rate was minus 16 per cent. The following day she

was depressed, despondent, wept readily and talked incoherently. That evening she was disoriented, entirely irrational, and refused fluids and food. The pulse rate had risen from her initial level of 70 to 92 per minute. During the next three days she was in a state of stupor alternating with a muttering delirium. Thyroid medication was discontinued. She gradually improved and in ten days her condition was similar to that on admission. Several weeks later she was given $\frac{1}{2}$ gr. of thyroid daily. Within a week some mental confusion developed which again disappeared when thyroid was withdrawn. At no time during the patient's illness were any focal signs of disease of the nervous system elicited.

Comment. The events observed in this patient can only be explained by assuming that she had latent cerebral arteriosclerosis with sufficient blood supply to the brain so long as the metabolism of this organ remained at a low level, but without the ability to adjust the cerebral vessels to the increase in blood supply which was needed when the metabolism of the brain tissue was increased by thyroid administration. (Since this patient was observed another myxedematous elderly subject with an identical reaction to thyroid and with recovery following its withdrawal has been observed).

DISCUSSION

The foregoing discussion is admittedly incomplete. My object has been to consider a group of allied disorders from an illustrative rather than from a comprehensive standpoint. A more complete exposition would have to include other disorders, such as acute mountain sickness for example. It is probable that in the future new clinical syndromes which fall into the general group of temporary disturbances of the balance between the oxygen supply and the oxygen need of the brain will be described. In any case it would seem that supplementing the usual etiologic and pathologic points of view by attempting a physiological approach will be helpful in understanding this complex but common and important group of conditions.

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COMPLEMENT TITRATIONS IN HUMAN SERA¹

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Complement or alexin can no longer be thought of as a single substance, for there is ample evidence that its activity in cellular or bacterial lysis and opsonization and in fixation in antigen-antibody combination depends upon one or more of the four components which have been identified with certainty. Hegedüs and Greiner (1) have pointed out that the "titer" of complement is limited by the quantity of component present in lowest titer. By separate titration of the four components these workers showed that the low titers obtained with unfractionated human complement were due to a marked deficiency in the second component or "endpiece." This kept the "titer" low even though the human sera contained even more first component (combining component or "midpiece") than did guinea-pig serum, the usual standard in complement studies. In human sera, then, complement titrations carried out in the usual way give the "endpiece" or second component titer and not that of the other components or of complement as a whole. This affords a possible clue to the failure of human complement "titers" to reflect clearly conditions of health and disease, for the behavior of the combining component, or first component, which is taken up in complement fixation, bacterial lysis, and hemolysis, would seem of greater interest. An independent method for the estimation of the combining, or first component, C'1, in absolute or weight units is now available (2) and data obtained with human complement by this method are being assembled for publication.

In the meantime complement titrations of human sera, affording a relative measure of the C'1 content, may be carried out by addition of crude guinea-pig "endpiece" (1). Guinea-pig complement components 2, 3, and 4 may be obtained even more simply as follows: For each milliliter of guinea-pig complement (serum) a specific precipitate is formed with about 0.02 mg. of egg albumin nitrogen and about 0.1 to 0.2 mg. of rabbit anti-egg albumin nitrogen, or with similar quantities of Type III pneumococcus specific polysaccharide and homologous rabbit antibody. These amounts of specific precipitate have been shown (2, 3) to remove the entire content of combining component, C'1, from complement. The mixture is centri-

¹ The work reported in this communication was carried out under the Harkness Research Fund of the Presbyterian Hospital.

fused as soon as the precipitate has flocked and the supernatant used as given below.

For the titrations given in the protocol use was made of 0.2 ml. of hemolytic system consisting of equal volumes of 5 per cent sheep red cell suspen-

PROTOCOL 1

Human complement titrations with and without reinforcement

HUMAN SERUM AND DILUTION USED	GUINEA- PIG SERUM SUPER- NATANT	HEMOLYSIS BY QUANTITY OF HUMAN SERUM DILUTION USED, ML.								
		0.05	0.075	0.1	0.15	0.175	0.2	0.225	0.25	0.3
B, 1:30	—			++	+++		ac	c		
Same, next day	—					+++		ac	ac	c
Same, next day	+			+++±	c	c				
C, 1:10	—						+++±	ac	c	
C, 1:30	+				+++	ac	c	c		
D, 1:10	—	+++		c						
D, 1:30	+			+++	ac		c	c		
Same, in CO ₂ snow 1 wk., 1:15	+	+++±	c							
1 ₀ , 1:10	—				++±		+++±		ac	
1 ₀ , 1:25	+			++±	ac	ac	c			
1 ₁ , 1:10	—			+++		c				
1 ₁ , 1:40	+	+++	ac	c						
2 ₀ , 1:10	—				+++±	ac				
2 ₀ , 1:40	+	+++	ac	c						
2 ₁ , 1:10	—			+++			+++±			c
2 ₁ , 1:40	+	+++	ac	c						
5 ₂ , 1:10	—			+++			ac			c
5 ₂ , 1:40	+	+++	ac	c						

Degrees of hemolysis: ++, +++, etc., ac = almost complete, c = complete.

Samples B, C, D were from cardiac patients; 1, 2, 5 from normals. Occasional sera, anticomplementary at 1:10, must be titrated at higher dilutions.

sion and a dilution of hemolysin containing two "units." 0.05 ml. of guinea-pig serum supernatant, prepared as indicated, was added to each tube containing the increasing volumes of diluted human serum to be titrated, followed by saline to 0.5 or 0.6 ml. total volume. Readings were taken after 20 to 30 minutes in a water bath at 37°C. The usual controls were run, including one with 0.1 ml. of the guinea-pig serum supernatant

with saline and hemolytic system. This showed 0 hemolysis in every case. For each serum the first line in the protocol shows the titration without added C' 2, 3, 4, while the second line indicates the result of addition of the guinea-pig serum supernatant as above.

The protocol shows that addition of adequate quantities of complement components 2, 3, and 4 from a guinea-pig serum supernatant deprived of its first component and incapable, by itself, of hemolyzing sensitized red cells, supplements the deficient components (C'2, according to Hegedüs and Greiner) in the human serum and permits hemolysis at higher titers. Normal human sera such as 1₀, or 2₀, titrated by themselves, appear to contain less than 40 to 60 "units" of complement per milliliter. However, when the deficiency in components other than C'1 is made up, the titers reach 125 to 400 "units" and become equal to those of typical guinea-pig serum. These titers then reflect the C'1 content, since the other components have been added in excess and the "titer" is still a measure of the component present in lowest "titer."

It may be debatable whether information of greater clinical value will accumulate from titrations of human C'1 with fortified complement than from the usual titrations, which yield data presumably only as to C'2. Possibly C'3 and C'4 should be titrated as well, and methods for doing this are available (1, 4). At any rate it is clear that unmodified "complement" titrations do not yield comparable information when carried out with guinea-pig and with human sera.

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ON MECHANISMS OF INSPIRATORY FILLING OF THE CERVICAL VEINS AND PULSUS PARADOXUS IN VENOUS HYPERTENSION

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The association of marked pulsus paradoxus with inspiratory filling of the cervical veins has been of value in the diagnosis of chronic constrictive pericarditis. Both of these "paradoxical" manifestations have been attributed to mediastinal adhesions because of the inflammatory and "adhesive" nature of this disease.

Wenckebach (1) regards the inspiratory weakening of the pulse in mediastino-pericarditis to be due to the adhesions which envelop the heart and attach it to surrounding structures. During inspiration, these structures spread apart and the resulting traction upon the heart interferes with its emptying. According to Gauchat and Katz (2), such adhesions serve as a plausible explanation for the genesis of pulsus paradoxus in certain cases of constrictive pericarditis. Its absence in other instances which came to necropsy was considered by them to be due to lack of adhesions to mobile portions of the thorax.

Adhesions about the large veins which may in a like manner interfere with their discharge during inspiration may also lead to diminished inspiratory filling of the heart and to inspiratory distention of the cervical veins. Although mechanical distortion of the superior vena cava may possibly explain the inspiratory swelling of the cervical veins, the presence of this physical sign in syndromes associated with venous hypertension (without mediastinitis) suggests that other mechanisms may also operate in its production.

Accurate observations of increased inspiratory filling of abnormally tense cervical veins by inspection and palpation are frequently difficult. Even in constrictive pericarditis there is only a small percentage of cases where inspiratory filling of the cervical veins is of sufficient prominence to allow clinical recognition. This phenomenon is more frequently and more accurately detected manometrically by actually measuring the venous pressure in cervical veins before and during a full deep inspiration.

This communication is based essentially upon venous pressure measurements obtained before and during inspiration in cases exhibiting venous hypertension. It will endeavor to correlate the "paradoxical" inspiratory elevation of the cervical venous pressure and the pulsus paradoxus with certain abnormalities in the circulatory and cardiopulmonary dynamics.

MATERIAL AND METHODS

The effect of deep inspiration upon the cervical venous pressure was observed in eight cases of constrictive pericarditis, in fourteen cases of right heart failure, in seven cases of superior vena caval obstruction, and in eighteen normal individuals. The occurrence of pulsus paradoxus in the above syndromes was also recorded.

The circulatory disturbance accompanying constrictive pericarditis, right heart failure, and superior vena caval obstruction was studied by measuring the venous pressure curve in the veins of the neck. The femoral venous pressure was also recorded in all cases of superior vena caval occlusion. The velocity of blood flow in circulatory pathways which included either the superior or inferior vena cava was determined with the ether and saccharin circulation time methods.

The venous pressure curve was determined by measuring the initial venous pressure in an external jugular vein during rest and during manual compression of the right upper abdomen for one minute. Following this, the effect of a full deep inspiration upon the initial venous pressure was recorded.

Respiratory undulations were also observed when the venous pressure was determined in an antecubital vein, but these undulations although showing parallel trends were not of sufficient magnitude to justify any clinical deductions. The weakness of the respiratory undulations was attributed to the relative insensitivity of the method employed. Fishberg (3) states that the undulations are damped by the great inertia of the blood column from the heart to the antecubital vein plus that of the manometric system. We have observed prominent respiratory undulations in an antecubital vein in patients with anemia and hypotension in whom the viscosity of the blood was reduced. To obtain maximum respiratory excursions of the venous pressure in a tributary of the superior vena cava the following points in technique must be fulfilled:

- 1) A large external jugular vein must be employed; the nearer the measurement is to the heart, the less will be the inertia of the blood column.

- 2) A large gauge needle must be used (18 gauge or preferably 16 gauge); the amplitude of the respiratory oscillations is directly related to the bore of the needle.

- 3) The patient must be told to take a full deep breath; a normal inspiration may not overcome the inertia of the blood column and consequently may not cause an appreciable respiratory fluctuation of the venous pressure.

Determination of the initial venous pressure in an external jugular vein. The initial venous pressure was measured directly by means of an L-shaped manometer moistened with 10 per cent sodium citrate (slight modification of Taylor, Thomas and Schleiter (4) technique). After the area was novocainized, the 16 to 18 gauge needle was inserted into a large

external jugular vein, the point of insertion being placed at the theoretical level of the right auricle (5 cm. below the anterior surface of the sternum). To facilitate venopuncture the subjects were ordered to strain as during micturition. When the rising or falling blood column in the manometer became stationary, the reading was recorded. The venous pressure with this method in a large series of "normals" ranged from 2 to 10 cm. of blood.

Effect of manual compression of the right upper abdomen. While the needle was still *in situ*, the right upper abdomen was compressed manually (about 30 to 40 lbs. pressure exerted with the palm of the hand) for

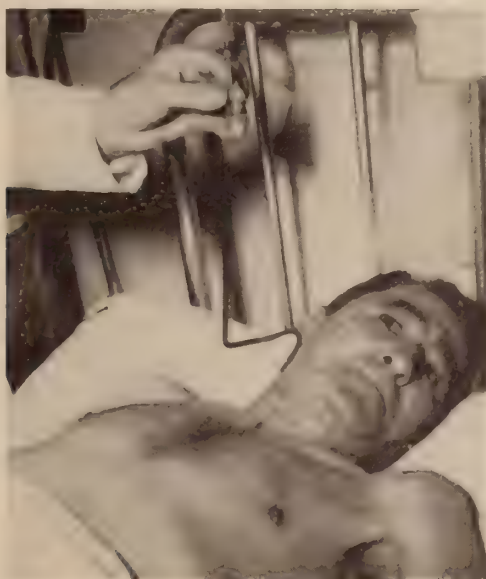


FIG. 1. Determination of initial venous pressure in external jugular vein. The manometer is attached to a rubber tube which at its distal end is leveled so that the zero-point corresponds approximately to the level of the right auricle.

one minute. The rise or fall of the blood column above or below the initial venous pressure was recorded. Normally, right upper abdominal compression caused a progressive fall of the external jugular venous pressure which ranged from 0.5 to 2.5 cm.

Effect of deep inspiration upon the external jugular venous pressure. While the needle was still *in situ*, the patient was told to take a slow deep full breath. The average effect of two inspirations upon the height of the initial venous pressure was recorded. To avoid erroneous results, the subject was told to relax and the manometer was tested for complete patency when the inspiratory observation was concluded, by manually compressing the cervical vein below the insertion of the needle or by having the subject strain.

The venous pressure in an external jugular vein during inspiration was measured in eighteen normal individuals. In all of these individuals there was inspiratory emptying of the cervical veins, the venous pressure falling during inspiration from 0.5 to 2.5 cm. When several (3 to 4) rapid successive deep inspirations were performed, the venous pressure dropped more markedly (4 cm. lowest drop).

Effect of a tourniquet applied to the chest wall upon the level of the initial venous pressure. After recording the effect of a deep inspiration, a Levine



FIG. 2. Determination of effect of manual compression of right upper abdomen. The right upper abdomen is compressed manually and the effect of this maneuver upon the level of the initial venous pressure after one minute of compression is recorded.

In this patient, who suffered from arteriosclerotic, rheumatic and possibly luetic heart disease (Wassermann test was 4 plus), the initial venous pressure was 22 cm. and right upper abdominal compression caused a further rise to 41 cm. On deep inspiration the cervical venous pressure rose $1\frac{1}{4}$ cm. That the hepatojugular reflux phenomenon was not a pure "liver" phenomenon was established by compressing the left lower abdominal quadrant and recording the rise. In this patient such a maneuver was followed by a rise of 18 cm. above the initial venous pressure level.

tube was applied to the entire circumference of the thorax at the level of either the nipples or the xiphoid process. The effect of this procedure upon the cervical or antecubital venous pressure was especially significant in cases of superior vena caval occlusion, a rise indicating interference with the superficial venous blood flow downward to the inferior vena cava (5). Normally, and in heart failure the thoracic tourniquet had no effect upon the initial venous pressure.

Determination of femoral venous pressure. The femoral venous pressure was measured primarily in superior vena caval obstruction. An elevated external jugular venous pressure in the presence of a normal femoral

venous pressure was regarded as pathognomonic of superior vena caval obstruction (8).

Circulation time. Circulation times with ether (6) and saccharin (7) were obtained from either cervical or antecubital veins in all cases. They were of value in establishing and differentiating the types of circulatory syndromes studied. For details of methods see the original papers. In a brief way, the ether time ("arm to lung time") measured the circulation time from an antecubital vein to the pulmonary arterial capillaries and was regarded as a measure of the right heart unit (normal $3\frac{1}{2}$ to 8 seconds). The saccharin time ("arm to tongue time") measured the circulation time



FIG. 3. Determination of effect of thoracic tourniquet applied at xiphoid level. In superior vena caval occlusion below the azygos vein, blood returns to the heart from the upper part of the body by means of circuitous collateral vessels which drain into the inferior vena cava. If the main pathway of returning blood is via the prominent superficial thoracic collateral channels (as will occur when the internal mammary vessels are also compressed by massive mediastinal metastases), application of a thoracic tourniquet will cause a progressive rise of the tension in the cervical or antecubital veins.

from an antecubital vein to the capillaries of the tongue (normal 9 to 16 seconds). The "lung to tongue time," obtained indirectly by subtracting the ether time from the saccharin time, yielded the circulation time from the pulmonary to the lingual capillaries and was regarded roughly as a measure of the left heart unit (normal $4\frac{1}{2}$ to 10 seconds). In superior vena caval occlusion the arm circulation time was also performed in some cases during manual compression of the abdomen in order to gain indirect information on the route of the collateral pathway (5). Circulation time measurements from the femoral vein were also obtained in the superior vena caval syndrome (normal "thigh to lung time" ranged between 4 and 9 seconds, and normal "thigh to tongue time" ranged between 9 and 17 seconds).

CHRONIC CONSTRICTIVE PERICARDITIS

In eight patients with chronic constrictive pericarditis, the venous pressure curve was found to be markedly abnormal and consisting of a high initial venous pressure with an associated marked rise during manual right upper abdominal compression. The elevation of the cervical venous pressure during right upper abdominal compression had as its clinical counterpart the "manual hepatojugular reflux" phenomenon of Pasteur (9) and Rondot (10). This phenomenon as measured quantitatively in centimeters of blood during one minute of compression yielded the highest value in cases of constrictive pericarditis. Its magnitude in this condition is dependent upon the severity of the right ventricular compression and the degree of systemic engorgement.

In all of these cases a deep inspiration was accompanied by a manometric rise of 0.5 to 3 cm. The rise, which occurred toward the end of inspiration, bore a direct relationship to the depth of the inspiration and to the muscularity of the subject. In most instances (6 cases) the inspiratory rise did not exceed 1.5 cm. In only two of these patients was the inspiratory rise of the venous pressure detectable clinically by visualization and palpation of the cervical veins.

The velocity of blood flow through the lungs as measured by the ether and saccharin circulation time methods was decreased, the retardation being much less marked, however, than in cases of universal heart failure (combined right and left). In four instances there was disproportionate slowing of the speed of blood flow in the "arm to lung segment" as compared to the "lung to tongue segment." Such differential circulation time readings were regarded as significant of predominant compression of the right side of the heart.

Inspiratory weakening of the pulse sufficient to be detected by palpation (or with the sphygmomanometer) was observed in only two cases. Its absence in six of the cases weakens but does not exclude the theory of mediastinal adhesions around the great veins (diminished inspiratory filling of the heart) as the cause of pulsus paradoxus.

UNIVERSAL HEART FAILURE (COMBINED RIGHT AND LEFT)

Inspiratory elevation of the cervical venous pressure was demonstrated in fourteen cases of right heart failure. Although the existence of this phenomenon was searched for in many other cases of right heart failure, its presence was noted only in severe cases manifesting the following characteristics:

- 1) The right heart failure cases were always secondary to failure of the left side of the heart. This was confirmed objectively by circulation time measurements which showed marked prolongation.

- 2) The right heart failure was always severe as indicated by a high

or moderately high initial venous pressure (19 to 36 cm.) and a further rise of the venous pressure during right upper abdominal compression (+15 to +20 cm.) (11). (This type of venous pressure curve was also characteristically obtained in constrictive pericarditis.)

As in constrictive pericarditis, the inspiratory rise of the cervical venous pressure in right heart failure occurred generally toward the end of inspiration and was followed by a fall of lesser magnitude toward the end of expiration. The inspiratory rise ranged between 0.5 and 2.0 cm. Pulsus paradoxus was not present.

Circulation time studies with ether and saccharin in these cases revealed a marked universal retardation of the speed of pulmonary blood flow. The "arm to lung time" ranged between 8 and 23 seconds and the "lung to tongue time" between 15 and 30 seconds. The retardation of blood flow in the venous and arterial components of the pulmonary pathway signified an increased cross-section of the pulmonary circulation. This fact, as will be shown later, may explain the absence of pulsus paradoxus in universal heart failure.

SUPERIOR VENA CAVAL OBSTRUCTION

Ten patients presenting the syndrome of superior vena caval obstruction were observed. Inspiratory filling of the cervical or antecubital veins was present in seven patients of this group. The rise in venous pressure ranged from 1.0 to 3.5 cm. The absence of inspiratory filling of the cervical veins in three of the patients despite the marked elevation of the venous pressure in tributaries of the superior vena cava can be ascribed to the fact that in these cases the collateral circulation was predominantly supra-diaphragmatic as occurs in obstruction above the azygos vein. The cases which showed an elevation of the cervical venous pressure during inspiration manifested a prominent superficial collateral circulation. Four of these patients came to autopsy and showed obstruction of the superior vena cava close to the heart (below or including azygos vein). In five of the seven patients the circulatory measurements indicated that the venous return from the upper half of the body was predominantly infra-diaphragmatic by means of circuitous pathways through the inferior vena cava as occurs in obstruction below the azygos vein. The abnormal circulatory measurements which suggested obstruction below the azygos vein were:

- 1) Prolongation of the "arm to lung time" and "arm to tongue time" in the presence of a normal "thigh to lung time" and "thigh to tongue time" (5).

- 2) Increased prolongation of the "arm to lung time" and "arm to tongue time" during manual upper abdominal compression (5).

- 3) Increased elevation of the antecubital or cervical venous pressure

when the superficial thoracic or abdominal collateral channels were compressed either by a thoracic tourniquet or by manual upper abdominal pressure.

These abnormal circulatory measurements imply that in caval obstruction below the azygos vein, the pathway of blood returning from the territory drained by the superior vena cava is via collateral veins which empty into the inferior vena cava. This does not obtain in high superior vena caval obstruction where the azygos vein becomes the main channel for blood returning to the heart from the upper part of the body. The route is shorter and more direct and the circulatory measurements may, therefore, not be significantly altered.



FIG. 4. Infra-red photograph showing marked collateral circulation due to mediastinal metastases from a prostatic carcinoma. Thoracic tourniquet and manual right upper abdominal compression caused a moderate rise of the antecubital venous pressure. Toward the end of inspiration the cervical venous pressure rose $1\frac{1}{2}$ cm. above the initial level and fell 1 cm. toward the end of expiration.

Pulsus paradoxus was not observed in any of the above cases although the "dynamic" form of pulsus paradoxus has been described by Wenckebach (1) in intrathoracic tumors. It was observed, however, following bronchoscopy in a recent case of bronchial carcinoma with marked tracheal stenosis. The phenomenon was associated with marked inspiratory stridor and inspiratory emptying of the cervical veins.

Paradoxical inspiratory elevation of the cerebrospinal fluid pressure (12), was recently observed in a case of superior vena caval obstruction due to metastases from teratoma of the testicle. As can be seen from table 1, elevation of the cerebrospinal fluid pressure (rise of 5.2 cm. of water) during inspiration was associated with an inspiratory elevation of

the antecubital venous pressure (rise of $1\frac{1}{2}$ cm.). The measurements performed by Dr. Kroop (12), were as shown in table 1.

In this case the inspiratory cerebrospinal fluid pressure elevation paral-

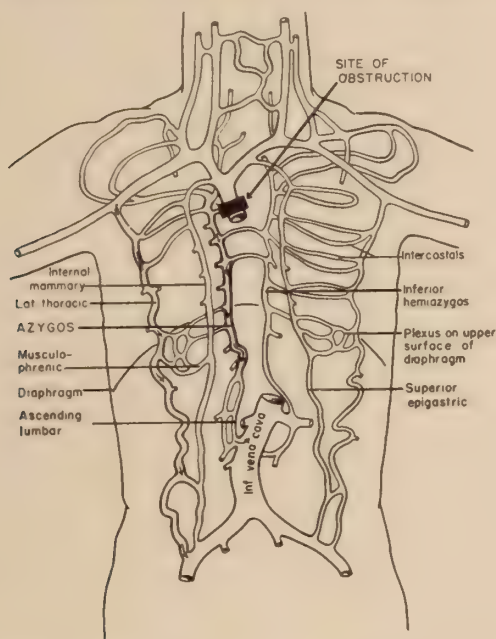


FIG 5. Obstruction of superior vena cava below (or including) azygos vein. Azygos vein and tributaries become smaller and show reversal of blood flow. All of the blood returns to the heart through the inferior vena cava. Schematic drawing of collateral circulation (after Blasingame).

TABLE 1

CEREBROSPINAL FLUID PRESSURE	VENOUS PRESSURE
Initial pressure—38.8 cm. of water	Initial pressure (right antecubital vein)—21.5 cm.
Deep inspiration caused a rise to 44.0 cm.	Right upper abdominal compression caused a rise to 25.5 cm.
Left jugular compression caused a rise to 52.0 cm.	Deep inspiration caused a rise of the antecubital venous pressure to 23.0 cm.
Right jugular compression caused a rise to 54.0 cm.	Normal respiration: inspiration, rise of $\frac{1}{4}$ cm.; expiration, fall of $\frac{1}{4}$ cm.
	Ether circulation time: right, 12; left, 21
	Saccharine circulation time: right, 27; left, 23

leled the antecubital venous pressure elevation during inspiration. This is significant because in normal individuals a deep inspiration is accompanied by a depression of the tension in the cerebrospinal fluid system and in the tributaries of the superior vena cava. The inspiratory rise in

the cerebrospinal fluid pressure must therefore be attributed to inspiratory interference with the brachio-cephalic venous return to the heart and may be regarded as comparable to a partial jugular vein compression effect upon the cerebrospinal fluid pressure. Similar inspiratory elevation of the cerebrospinal fluid may therefore be expected in those cases of constrictive pericarditis, right heart failure, or pericardial effusion which manifest the cervical or antecubital vein phenomenon during deep breathing. This is in agreement with the work of Weed and Hughson (13) who have shown that the cerebrospinal fluid tension is largely dependent upon the venous pressure.

DISCUSSION

Although mediastinal adhesions may be a cause of inspiratory filling of the cervical veins and of pulsus paradoxus in isolated instances of constrictive pericarditis, the presence of these phenomena in unrelated conditions suggests a circulatory or cardio-respiratory basis for their genesis rather than a purely mechanical one.

Katz and Gauchat (2) have shown experimentally that traction anywhere on the pericardial structures may produce a pulsus paradoxus, the presence of which depends upon the tension rather than upon the location of the "adhesions." Time relations showed that such a pulsus paradoxus was always the direct or indirect result of partial occlusion of the pulmonary vessels and aorta, but never due to compression of the venae cavae. Inspiratory elevation of the cervical venous pressure may therefore be regarded as a phenomenon dynamically independent of pulsus paradoxus in constrictive pericarditis. The mechanisms involved in the causation of these paradoxical phenomena in conditions associated with venous hypertension will be presently discussed.

Inspiratory filling of the cervical veins may occur not only in chronic constrictive pericarditis, right heart failure, and superior vena caval occlusion, but probably also in pericardial effusion. Cases of pericardial effusion have come under observation in which the initial venous pressure was markedly elevated and the "manual hepatojugular reflux" phenomenon was unusually prominent. Inspiratory filling of the cervical veins was not demonstrated manometrically in these cases. In a recent case of cardiac tamponade on the basis of rheumatic fever, "pulsus paradoxus" was present, but inspiratory filling of the cervical veins, although probably present, was not visibly nor palpably discernible. The initial venous pressure was very high but the veins were too tense to allow observations of slight pressure changes clinically. Even an augmented inspiration failed to alter the tension in these veins significantly, although such breathing engendered a more prominent "pulsus paradoxus."

The mechanism causing inspiratory filling of the cervical veins in constrictive pericarditis, and in right heart failure, (and possibly also in

pericardial effusion) is in diametric contrast to the mechanism which is responsible for the appearance of this phenomenon in cases of superior vena caval occlusion. In the former conditions, it is associated with central venous stasis due to the increased venous return to the heart during inspiration while in superior vena caval obstruction there is no central venous stasis and the inspiratory venous return may actually be diminished due to interference with the collateral circulation. In all of these conditions the inspiratory filling of the cervical veins is associated with a marked elevation of the venous pressure in the neck veins during right upper abdominal compression. This suggests an identical mechanism for the causation of the increased elevation of the venous pressure in the

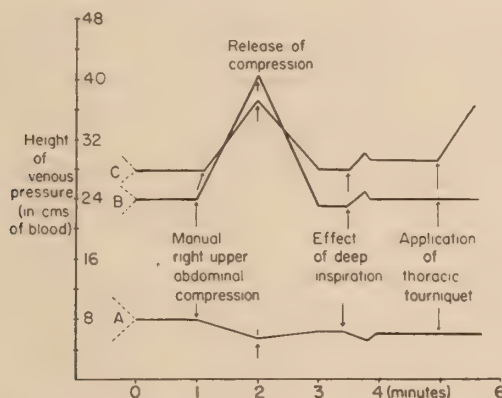


FIG. 6. Cervical venous pressure curves in (A) "normals," (B) right heart failure (combined) marked degree and (C) superior vena cava obstructions (below azygos vein).

In superior vena caval obstruction (below azygos vein), manual compression of right upper abdomen, application of thoracic tourniquet and deep inspiration will cause a rise of the cervical venous pressure due to interference with the collateral pathway through the inferior vena cava.

neck veins during inspiration and during manual compression of the abdomen.

The "manual hepatojugular reflux" phenomenon in constrictive pericarditis, right heart failure, and pericardial effusion is due to a marked elevation of the intra-abdominal pressure which causes an enormously increased venous return to the heart. The overloading effect of the right heart during abdominal compression is promptly transmitted to the veins of the neck where it manifests itself clinically by marked distention of the neck veins or manometrically, by a marked elevation of the venous pressure. A full deep inspiration in these "congestive" states may simulate in a less forceful way the right upper abdominal compression phenomenon by increasing the venous return centrally, overloading the inefficient right heart, and thereby effecting a slight but significant "paradoxical" in-

spiratory elevation of the venous pressure in the veins of the neck ("inspiratory hepatojugular reflux phenomenon").

The "inspiratory hepatojugular reflux phenomenon" in systemic venous hypertension is not really "paradoxical" for it has a sound physiologic basis. Its causation is based upon alterations of the circulatory but not the respiratory dynamics. Normally and in heart failure the diaphragm descends during inspiration and the tonus of the abdominal muscles is strengthened. This leads to an increased negative pressure in the chest cavity and to an increased positive pressure in the abdomen. This increased difference in pressure is effective in aspirating blood from the superior vena cava and in driving blood from the abdomen (liver and tributaries of the portal vein) into the right heart.

Whether or not the cervical veins fill during inspiration is determined largely by the circulatory adjustments that ensue between an augmented venous return and the ability of the right heart to handle it. In healthy individuals, the normal right heart, in accord with Starling's law, accommodates itself promptly to the increased venous return, but the venous pressure, after the initial "venous thrust," falls in tributaries of the superior vena cava because the maintained manual compression of the inferior vena cava subsequently reduces the venous return from the caudal regions of the body. In "congestive" states, however, the venous return from the liver and portal tributaries is enormously increased not only because of the greater circulating blood volume in heart failure, but also because of the disproportionate accumulation of blood in the intra-abdominal blood depots, especially in the liver (3). As a consequence, the insufficient or compressed right heart is overloaded beyond its functional capacity. The central venous stasis (large veins and right auricular stasis) that follows, promptly retards the venous influx from the superior vena cava and as a consequence the "inspiratory hepatojugular reflux phenomenon" gradually makes its appearance.

The "inspiratory hepatojugular reflux phenomenon" in these cases is due solely to the altered circulatory dynamics and not to mediastinal distortion. That it is a pure "congestive" phenomenon was further established in four of the cases in whom venous pressure measurements were repeated after cardiac compensation was considerably improved with bed rest, digitalis, ammonium chloride and mercurial diuresis (see table 2). In all of these cases the "inspiratory hepatojugular reflux phenomenon" did not only fail to appear despite the persistence of a moderate "manual hepatojugular reflux phenomenon" but a deep inspiration was accompanied by an actual fall of the external jugular venous pressure.

In superior vena caval obstruction below the azygos vein the mechanism which causes an inspiratory rise of the cervical venous pressure also parallels the mechanism which causes elevation of the cervical venous pressure when the abdomen is compressed. The rise of the cervical venous pres-

sure during manual upper abdominal compression in superior vena caval obstruction does not result however, from an overloading of the right heart by an increased venous return as occurs in right heart failure. The venous return to the heart may be actually diminished when the abdomen is compressed. The increased filling of the veins in the neck results from the increased intra-abdominal tension or from compression of the inferior vena caval pathway which transports the blood returning from the upper part of the body.

Inspiratory filling of the cervical veins in complete superior vena caval obstruction (below the azygos vein) has a similar origin. The inspiratory descent of the diaphragm increases the intra-abdominal pressure which

TABLE 2

Disappearance of "inspiratory hepatojugular reflux phenomenon" after cardiac therapy in universal heart failure

DIAGNOSIS	DECOMPENSATION BEFORE CARDIAC THERAPY			RELATIVE COMPENSATION AFTER CARDIAC THERAPY		
	Initial venous pressure, cm. of blood	"Manual hepatojugular reflux," cm. of blood	"Inspiratory hepatojugular reflux," cm. of blood	Initial venous pressure, cm. of blood	"Manual hepatojugular reflux," cm. of blood	"Inspiratory hepatojugular reflux," cm. of blood
Coronary artery disease	23	Present; rise of 19	Present; rise of $1\frac{1}{2}$	10	Present; rise of 7	Absent; fall of $1\frac{1}{2}$
Chronic rheumatic cardiovascular disease	25	Present; rise of 18	Present; rise of 2	13	Present; rise of 9	Absent; fall of 2
Hypertensive and arteriosclerotic heart disease	20	Present; rise of 16	Present; rise of 1	9	Present; rise of 6	Absent; fall of 1
Coronary artery disease	19	Present; rise of 19	Present; rise of $1\frac{1}{2}$	$8\frac{1}{2}$	Present; rise of 3	Absent; fall of $2\frac{1}{2}$

squeezes blood out of the liver and portal tributaries but compresses the inferior vena cava. Inspiration interferes in this way with the return flow of blood through the circuitous abdominal pathways and the venous pressure in the tributaries of the superior vena cava consequently rises.

Pulsus paradoxus. Kussmaul (14) termed the inspiratory weakening of the pulse in mediastinal pericarditis as "pulsus paradoxus" because he observed it occurring while the heart continued to beat steadily and strongly with no respiratory variation. This phenomenon occurs classically in pericardial effusion, where it is of diagnostic value. Its presence even during natural breathing is especially remarkable because patients who exhibit it frequently present no clinical evidence of respiratory discomfort, although their radial pulse during inspiration may decrease in amplitude to the point of almost complete inpalpability.

Katz and Gauchat (2) studied the "pulsus paradoxus" experimentally and attributed its origin in pericardial effusion to the following mechanism: "When the pericardium is distended with fluid not only is the flow of blood into the heart impeded, but the inflow also varies during inspiration and expiration, owing to the fact that the respiratory variations of intrathoracic pressure do not affect the intrapericardial and intracardial pressures as much as those in the entering veins. This would naturally cause a small difference of pressure between the veins and heart during inspiration and allow less filling of each ventricle. Consequently, a paradoxical pulse would probably appear in both the pulmonary and systemic circuits but the arterial pulsus paradoxus would result from the impaired flow into the left ventricle.

An inspiratory decrease in the effective venous pressure within the large mediastinal veins, leading to diminished filling of the right ventricle, may serve as a plausible explanation for pulsus paradoxus in pericardial effusion. In normal individuals, the effective venous pressure is not decreased during inspiration, because the negative effects of a decreased intrathoracic tension are neutralized by equal reduction of pressures around the veins, auricles, and pulmonary vessels. If a decreased intrathoracic pressure in pericardial effusion does exert a greater negative effect on the mediastinal veins than on intrapericardial and intracardiac pressures, how can the differential pressure concept of Katz and Gauchat (2) be reconciled with the phenomenon of inspiratory filling of the cervical veins as it occurs, for example, in cardiac compression associated with constrictive pericarditis (assuming that it is not due to adhesions)?

The occurrence of inspiratory elevation of the cervical venous pressure in constrictive pericarditis suggests that the effective venous pressure for filling the right heart may in these cases actually be increased rather than decreased during inspiration. The same alteration of the circulatory dynamics may prevail in hypodiastolic heart failure due to pericardial effusion. The venous return engendered during inspiration evidently preponderates over the depressing effect of the decreased intrathoracic pressure, and the venous pressure in the veins entering the heart rises rather than falls. Such increased elevation of the previously existing superior vena caval hypertension (as measured in the neck veins) during inspiration weakens but does not disprove the Katz and Gauchat (2) concept of the genesis of pulsus paradoxus.

Another concept which embodies normal cardio-respiratory mechanisms is therefore proposed. Accordingly, pulsus paradoxus may be regarded not as a paradoxical phenomenon, but as a physiologic accentuation under certain abnormal conditions of the mechanism which causes normal respiratory variations of systemic arterial pressure. In normal individuals the arterial pressure may be rhythmically elevated and decreased during the acts of respiration. Heinbecker (15) has shown that the respiratory

waves in systemic arterial pressure consist of an immediate fall on inspiration and an immediate rise on expiration. Hamilton, Woodbury, and Vogt (16) concluded from their experiments that the expiratory increase in systemic arterial pressure is caused partly by an increase in intrathoracic pressure and partly by an increase in cardiac output. Such respiratory variations of systemic arterial pressure and of left ventricular output obviously bear a direct relationship to the varying vascular capacity of the lungs during these respiratory phases.

Elucidation of the dynamics of the pulmonary circulation as they may affect the normal systemic arterial fluctuations during inspiration and expiration will shed more light, as will be shown later, on the genesis of pulsus paradoxus. The pulmonary circulation is affected by the following factors:

- 1) The systolic discharge of the right ventricle.
- 2) The degree of negativity of the intrathoracic pressure during inspiration and expiration which also determines
 - a) the pulmonary peripheral resistance offered by intrapulmonary and extrapulmonary vessels, and
 - b) the pulmonary vascular capacity during inspiration and expiration.

Experimental evidence (17) supports the view that during natural breathing the pressures in the pulmonary artery and vein will fall during inspiration and rise during expiration. The pulmonary arterial pressure falls during inspiration not because the right ventricular output is lowered, but because the decreased negative intrathoracic pressure is accompanied by an increased capacity of the extra-pulmonary and possibly intrapulmonary vessels.

The question of decreased pulmonary peripheral resistance during inspiration has given rise to considerable controversial opinion. Although lung perfusion experiments show clearly that an expansion due to decreased external negative pressure causes a fall of pulmonary arterial pressure and increased flow, Hamilton, Woodbury and Vogt (16) found that the pressure gradients between pulmonary arteries and veins during inspiration remain essentially unaltered. They concluded that in naturally breathing animals, reduction of pulmonary peripheral resistance is not a factor in the decline of pulmonary arterial pressure during inspiration. Wiggers (17), therefore, maintains that the chief cause of the fall of pressures in the pulmonary artery and right ventricle is the effect of reduced intrathoracic pressures on the larger extrapulmonary arteries.

The fluctuating pulmonary vascular capacity during inspiration and expiration probably determines the normal respiratory variations of systemic arterial pressure. The lag in the left ventricular output during inspiration may be attributed to the increase in capacity of the pulmonary vessels during inspiration. Heinbecker (15) has shown that the blood

temporarily pools in the more capacious blood vessels and is not delivered to the left heart until the following expiration. The "blood holding capacity" of the lungs during inspiration is governed by:

- 1) The degree of increased negative intrathoracic pressure which determines the total pulmonary vascular capacity during inspiration.

- 2) The "pulmonary blood volume" during expiration.

The "blood holding capacity" of the lungs during inspiration may therefore be regarded as the quantitative difference between these two factors.

The dynamics of the pulmonary circulation are well summed up by Wiggers (17) in an earlier edition of his book: "The decreased intrathoracic pressure during natural inspiration diminishes the peripheral resistance in the pulmonary capillaries which, together with a moderate distention of extrapulmonary arteries, accounts for the decrease in pulmonary arterial pressures during inspiration. At the same time however, the increased capacity of both extrapulmonary and intrapulmonary vessels results in accumulation of blood in the lungs and a transient decrease in flow to the left auricle. During each succeeding expiration, the pulmonary vessels are again emptied of their surplus blood and an increased onflow to the left auricle occurs."

The circulatory dynamics of pericardial effusion affect the pulmonary circulation in the following manner. The right heart which acts as a valve for the left heart maintains, because of the tamponade, a constant, markedly reduced, right ventricular output during both phases of respiration. As a result, the systemic venous circuit becomes distended with blood, but the pulmonary bed which normally can accommodate one-eighteenth of the blood volume during expiration and one-twelfth during inspiration (Starling) remains "relatively anemic." This explains the absence of signs of pulmonary engorgement and the relative respiratory comfort of the patients (provided that the cardiac tamponade does not exceed a critical level). Whether or not pulsus paradoxus will appear will depend largely upon the amount of blood propelled into the lungs as compared with the pulmonary blood volume under normal conditions. Because the small and constant "right ventricular discharge" establishes a small expiratory pulmonary blood volume and because the inspiratory vascular capacity of the lungs remains relatively normal, the inspiratory "blood holding capacity" of the lungs becomes disproportionately increased. Consequently, more of the blood that is expelled by the right heart will be held up in the lungs to fill the dilated capacious vessels during inspiration and less therefore will reach the left heart. The left ventricular output during this phase of inspiration will become proportionately lessened and a "paradoxical" pulse of varying degree will then appear. The time relations of the appearance of pulsus paradoxus established experimentally by Katz and Gauchat (2) is in harmony with the above concept. The prompt disappearance of the paradoxical pulse after tapping the pericardial effusion

is also compatible with such a concept. The increased right ventricular output following release of the heart will cause an increase in the blood volume content of the lungs and a proportionate decrease in its inspiratory "blood holding capacity."

The relationship of the blood volume content of the lungs during expiration to the pulmonary vascular capacity during inspiration may likewise explain the phenomenon of pulsus paradoxus in chronic constrictive pericarditis. This explanation would especially hold true for cases with predominant right-sided cardiac compression; the absence of this phenomenon in cases with predominant left-sided cardiac compression would be attributed to the increased cross-section of the pulmonary circulation due to backward failure of the left heart. Inspiration could not significantly increase the capacity of previously distended intrapulmonic and extrapulmonic vessels. Consequently, the marked discrepancy between the inspiratory vascular capacity and the expiratory blood volume which is necessary for the production of paradoxical pulse would be considerably dampened, and the rhythmic respiratory pulse would therefore fail to appear.

This concept also offers a logical explanation for the "dynamic" form of pulsus paradoxus as proposed by Wenckebach. A notable example of the dynamic form is laryngeal stenosis. Because the respiratory phases become enormously exaggerated in this condition, inspiration is accompanied by an abnormally high negative intrathoracic pressure which would increase markedly the inspiratory vascular capacity of the lungs. The "inspiratory blood holding capacity" of the lungs would therefore become disproportionately elevated as in pericardial effusion, the only difference being that the pulmonary blood volume during expiration would remain either within normal or subnormal limits but the pulmonary vascular capacity during inspiration would be abnormally increased.

The dynamic form of pulsus paradoxus differs from the paradoxical pulse of cardiac compression (as occurs in constrictive pericarditis and pericardial effusion) in the following manner:

1) It is not accompanied by systemic venous congestion (unless it is complicated by coexisting superior vena caval obstruction).

2) It is accompanied by inspiratory emptying of the cervical veins (unless it is complicated by coexisting superior vena caval obstruction).

The paradoxical pulse due to anatomic peculiarities must not be confused with the pulsus paradoxus of cardiac compression or of intrathoracic tumors. In healthy people a deep inspiration may elevate the thorax in such a way as to cause the subclavian artery to become nipped between the first rib and the clavicle and thereby reduce or abolish the radial pulse. This type of inspiratory weakening of the pulse may be established by demonstrating its presence only when the upper extremity is in certain positions. Furthermore, in true pulsus paradoxus all the pulses of the

body decline or fail but in the "anatomic" type the inspiratory weakening will be confined to the pulse of the involved area.

CONCLUSIONS

1) Inspiratory filling of the cervical veins is a non-specific phenomenon; it occurs not only in chronic constrictive pericarditis, but also in syndromes of venous hypertension (without mediastinitis) such as severe right heart failure (combined type) and superior vena caval obstruction. It is of diagnostic significance in chronic constrictive pericarditis only when it is accompanied by a pulsus paradoxus.

2) The "paradoxical" phenomenon of inspiratory filling of the cervical veins can be demonstrated manometrically by measuring the venous pressure in the veins of the neck. The elevation of the cervical venous pressure in the syndromes studied ranged from $\frac{1}{2}$ to $3\frac{1}{2}$ cm.

3) Manometric observations reveal that inspiratory filling of the neck veins occurs much more frequently than is clinically suspected. This is due to the fact that pre-existing elevation of the venous pressure interferes with the clinical evaluation of increased distention of the cervical veins during inspiration.

4) Inspiratory filling of the cervical veins in heart failure represents an imbalance between an abnormally augmented venous return from the abdomen and a diminished right ventricular output. The central venous stasis which surrounds an overloaded right heart retards the venous return from the upper part of the body. This is promptly reflected in tributaries of the superior vena cava, where it causes either visible filling of the veins or manometric elevation of the venous pressure.

5) Inspiratory filling of the cervical veins in superior vena caval obstruction occurs when the circulatory dynamics indicate that the closure is below the azygos vein. In these cases, the inspiratory descent of the diaphragm compresses the inferior vena cava and retards the blood flow through the collateral circulation and the intra-abdominal veins.

6) Paradoxical elevation of the cerebrospinal fluid pressure paralleling the inspiratory rise of the antecubital venous pressure was observed in one case of superior vena caval obstruction. It is suggested that a similar cerebrospinal fluid phenomenon will appear in those "congestive" states which manifest inspiratory filling of the cervical veins (clinically or manometrically).

7) A concept is proposed in explanation of the genesis of pulsus paradoxus in pericardial effusion. The phenomenon, which may be regarded as a functional exaggeration of normal cardio-respiratory dynamics, will appear when there is a marked discrepancy between the pulmonary blood volume during expiration and the pulmonary vascular capacity during inspiration. This concept can be similarly applied to constrictive peri-

carditis when the compression is predominantly right-sided and to the "dynamic" forms of pulsus paradoxus associated with laryngeal and intra-thoracic tumors.

8) The mechanical concept of the cause of inspiratory filling of the cervical veins and pulsus paradoxus cannot be ignored in some cases of constrictive pericarditis, but its occurrence in syndromes of venous hypertension (without mediastinitis) favors the cardio-respiratory or dynamic concept.

9) A "paradoxical pulse" that appears only in certain positions of the arm occurs as a result of abnormal anatomical relations between the sub-clavian artery and the first rib and the clavicle. The inspiratory weakening of the pulse is localized to the involved extremity in contrast to the generalized "pulsus paradoxus" of cardio-pulmonary origin.

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TREATMENT OF ATONIC' NEUROGENIC' BLADDER BY TRANSURETHRAL RESECTION

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For many years cases of urinary retention were clinically divided into two main groups, the obstructive and the non-obstructive. The former and by far the larger group of patients were those who exhibited manifest enlargement of the prostate gland or contracture of the bladder neck. The latter group consisted of a heterogeneous collection of cases generally spoken of as "neurogenic bladders." The obstructive cases were subjected to the various surgical procedures with eminently good end results. The non-obstructive retentions formed a difficult urological problem and their treatment was generally unsuccessful.

Our knowledge of the physiology and neurophysiology of the bladder and of the act of micturition has been greatly increased in the last two decades. This has largely been due to studies of the nerve supply (Elliot, Letarjet, Langworthy, Learmonth, etc.) and to the studies of cystometry (Rose, Muschat, Simons, McClellan, etc.). Their investigations of the bladder in animals as well as in man in both the normal state and in pathological lesions involving the various parts of the central and peripheral nervous systems have not only helped urologists in the diagnosis of various bladder conditions but conversely have also helped diagnosis of spinal cord lesions by cystometric studies of the bladder.

NERVE SUPPLY OF THE BLADDER; THREE DIFFERENT SETS OF NERVES CONTROL THE ACT OF MICTURITION

THE SYMPATHETIC NERVES. These arise from the thoraco-lumbar outflow and pass down in front of the aorta. There are ramifications with the coeliac and mesenteric ganglia as well as with the renal plexuses. Just below the bifurcation of the aorta the nerves group to form the presacral nerve (or nerves). This then divides into right and left hypogastric nerves which pass to the respective inferior hypogastric ganglia and thence to the bladder. It is believed that these cause relaxation of the bladder wall. In man, stimulation of the intact and distal end of the presacral nerve has resulted in contraction of the trigone and ureter orifices. Most investigators feel that the sympathetic nerve supply is of little importance. Section of the presacral nerve hardly alters the act of micturition.

THE PARASYMPATHETIC NERVES. These arise from the second, third and fourth sacral cord segments to form the pelvic nerves which then pass

through the hypogastric ganglia to the bladder. These nerves cause contraction of the detrusor, relaxation of the internal bladder sphincter and carry the sensory supply from the bladder. This is the main and most important nerve supply of bladder function.

THE INTERNAL PUDENDAL NERVES. These arise from the third and fourth sacral cord segments and after passing through the obturator canal, supply the voluntary or external urethral sphincter.

THE NORMAL AND ABNORMAL BLADDER

The normal bladder is capable of transmitting to the higher centers such sensations as filling, emptying, pain, touch and temperature. Although Learmonth (1) demonstrated that stimulation in man of the central end of the cut presacral nerve produced pain in the bladder region, most investigators believe that the main sensory supply is carried through the parasympathetic system.

The normal bladder on cystometric examination yields the following information. The first desire to urinate occurs after the introduction of 100 to 150 cc. of water into the bladder. Its maximum capacity varies between 350 and 450 cc. with a progressive rise in the intravesical pressure as the bladder is distended to from 1 to 8 or 15 cm. of water. With the bladder filled, voluntary straining to empty the organ will result in a rise of the intravesical pressure to between 60 and 90 cm. of water. There are no uninhibited contractions of the bladder wall. Sensations of filling and emptying are intact. Voiding after initiation continues with an uninterrupted stream.

If one excludes inflammatory lesions of the bladder wall, a hypertonic bladder will transmit the first desire to void when less than 100 cc. of fluid are introduced into the bladder. The intravesical pressure rises rapidly and sharply as the bladder content increases. Further distension may result in acute pain and evacuation of the bladder fluid around the catheter. The characteristic features are: 1) reduced capacity; 2) early rise in intravesical pressure; 3) pain on distension of the bladder; 4) uninhibited emptying of the bladder; and 5) slight if any residual urine.

Hypotonic and atonic bladders have a markedly increased capacity. There is absence of sense of fullness and a very low intravesical pressure even after the introduction of large amounts of fluid into the bladder. Voiding is accomplished with great abdominal straining and difficulty. The stream is usually interrupted. Residual urine is generally present. Overflow incontinence occurs after the maximum bladder capacity is reached. Patients with longstanding prostatic obstructions and large residual urine may exhibit a similar cystometric curve. McClellan thinks that this may be due to temporary injury of the bladder wall ganglia. Such bladders, however, usually show a different cystometric curve after

the bladder has been kept empty for several days with an indwelling urethral catheter.

FOUR TYPES OF NEUROGENIC BLADDERS ACCORDING TO MCCLELLAN (2)

1. **THE UNINHIBITED NEUROGENIC BLADDER.** This results from lack or loss of cerebral inhibition, either from failure of development (adult enuretic, morons and degenerates); unilateral cortical disease (hemiplegia, unilateral brain tumor); or subtotal destruction of the spinal cord pathways (early multiple sclerosis and pernicious anemia). Micturition is imperative but voluntary. Sensory pathways are intact.

2. **THE REFLEX NEUROGENIC BLADDER.** This results from widespread disease of the upper motor neurons from destruction of the cortex, spinal cord pathways or from complete section of the cord (above the sacral segments). Micturition is purely reflex and imperative or precipitate. Sensation is abolished. Examples of this type are:

A. Fracture of the vertebra with traumatic myelitis (above sacral segments).

B. Inflammatory lesions: acute myelitis, encephalomyelitis, extradural abscess, intradural abscess, chronic arachnoiditis, Pott's disease.

C. Neoplasm: vertebra, meninges, cord.

D. Diffuse pathological lesions: pernicious anemia, multiple sclerosis, arteriosclerosis.

E. Ruptured nucleus pulposus.

F. Bilateral cordotomy.

G. General anesthesia.

3. **THE AUTONOMOUS NEUROGENIC BLADDER.** This results from nuclear or infranuclear lesions of the sacral cord, cauda equina or sacral plexus with interruption of both afferent and efferent fibers of the reflex arc. There is absence of normal voluntary or reflex micturition. Sensation is abolished. Examples of this type are:

A. Traumatic lesions of lumbosacral spine: sacral segments, conus, cauda equina.

B. Inflammatory lesions: intra and extradural abscess, chronic arachnoiditis, sacral radiculitis.

C. Neoplasm: sacral cord, hypogastric plexus.

D. Congenital anomalies: myelomeningocele, spina bifida with involvement of cauda.

E. Spinal anesthesia.

4. **THE ATONIC NEUROGENIC BLADDER.** This results from lesions of the posterior sacral roots with interruption of the afferent fibers of the reflex arc. There is absence of normal, voluntary or reflex micturition. Sensation is abolished. Examples,

A. Tabes dorsalis

B. Certain cases of pernicious anemia and multiple sclerosis

- C. Diabetes
- D. Syringomyelia
- E. Progressive muscular atrophy
- F. Spinal shock (acute traumatic myelitis)
- G. Hysteria

One must remember that there are instances of myogenic vesical dysfunction which simulate and must be differentiated from the true neurogenic bladders.

Cases of hypotonic and atonic neurogenic bladders have been treated by transurethral resection with unusually good end results. We have had a number of these cases at this hospital. Similar cases have also formed the subject of an interesting paper by Emmet (3). The underlying principle is to remove any obstruction at the bladder neck or in the urethra no matter how minimal it may appear on cystoscopic examination. Even a normal internal sphincter may be resected. The purpose of this procedure is to allow the weak bladder detrusor with the aid of intra abdominal pressure to expel the bladder contents through the least possible resistance. One need have no fear of incontinence after such properly performed resections, provided there is no true prior incontinence. True incontinence signifies loss of external control and a loss of urine from the bladder as fast as it enters the organ. These cases show no residual urine. The paradoxical or overflow incontinence cases are incontinent in the presence of residual urine.

The following case of atonic neurogenic bladder is reported for its unusual clinical features as well as for the excellent result that followed transurethral resection.

CASE REPORT

History (Adm. 462774). M. T., a sixty-three year old man was admitted to The Mount Sinai Hospital September 18, 1940 complaining of lower abdominal distension and urinary retention. For over fifteen years he felt that he could not empty his bladder and had to press on his abdomen suprapubically in order to pass urine. This urinary difficulty dated back to 1925 when he was admitted to the neurological service of this hospital with a ten weeks' history of weakness of the left lower extremity, urinary difficulty and frequency. General physical examination at that time showed no abnormality. Neurological examination (1925) revealed the following: Cranial nerves, normal. Gait, spastic. Romberg sign, positive. Motor: Upper extremities, normal; lower extremities, hypertonic, the left more than the right; heel-to-knee test impaired. Reflexes: Upper extremities, normal; lower extremities, hyper active knee and ankle jerks; Babinski sign present on the right side; lower abdominals absent. Sensory: Hyperalgesia on the left side D4 to D7 and on the right side D4 to D5; touch, normal; impaired position sense in both feet; impaired vibration sense over left malleolus. Cerebrospinal fluid examinations, normal in every respect. Blood Wasserman reaction, negative. Cystoscopic examination, no abnormality in the bladder neck or posterior urethra. Residual urine, not tested. It was the consensus of opinion at that time that this patient suffered from a spinal cord tumor, although one of the neurologists felt that the patient had degenerative disease of the

spinal cord. Operation for spinal cord tumor was advised but the patient refused and left the hospital against advice.

His present complaints of urinary retention with over 1000 cc. of residual cloudy urine dated back for several weeks. This large infected residual urine was found in the course of investigation for the presence of a low grade fever.

Examination. The general physical status failed to show any gross abnormality except for a distended lower abdomen. Catheterization of the bladder yielded 26 ounces of turbid, purulent residual urine.

Neurological examination (Sept. 19, 1940 by Dr. M. Bender) disclosed the following positive findings: Gait: Spastic, ataxic, broad based and favoring the left leg. Coordination: Impaired heel-to-knee test. Reflexes: Hyperreflexia of both lower extremities. Bilateral Babinski, Chaddock, Rossolimo, Mendel-Beechterew signs. Lower abdominal reflexes were absent. Motor power: Paraparesis with the left more so than the right. Sensation: Vibration sense lost at and below both iliac crests. Position sense impaired in both feet. Temperature sense involved below D11 on the right side. Left side less involved. Pain sense involved same distribution as temperature but to a lesser degree. Cerebrospinal fluid. Manometric studies and other examinations were normal.

It was the opinion of Dr. Bender that this patient suffered from intramedullary cord disease with the highest level at D7. Since this patient's main complaint was that of urinary difficulty, other studies were performed. The blood urea nitrogen, complete blood count, blood pressure and the upper urinary tract on both sides were normal. Cystometry revealed a markedly atonic bladder muscle. There was no sensation of bladder fullness or pressure after introducing over 700 cc. of water into the bladder. With this amount there was no rise in intravesical pressure above the base line.

Cystoscopy showed a trabeculated bladder wall, slight inverted "V" formation at the anterior sphincter margin and very slight intrusion of the lateral lobes of the prostate intraurethrally.

Operation (September 25, 1940). A bilateral vasectomy was performed followed by a transurethral resection with the removal of 10 grams of tissue from the bladder neck and urethra. This tissue was reported by the laboratory as "fragments of fibroadenoma of the prostate."

Course. The indwelling catheter was removed after several days. He was given Doryl by mouth and injection. He voided in varying amounts but there remained a residual urine of 10 to 15 ounces.

Operation (October 3, 1940). A second transurethral resection was performed under spinal anaesthesia and an additional 11 grams of tissue were removed from the sphincter and posterior urethra.

Course. After removal of the indwelling urethral catheter the patient voided more easily than he had for years. He was discharged from the hospital October 11, 1940 for further treatment at the office. His residual urine dropped to less than one ounce. When he voided he passed a good stream which was interrupted and was dependent for its force upon the pressure of the abdominal wall musculature. With the use of sulfonamide medication his pyuria cleared up and the urine became crystal clear. At the present time he voids every three and four hours during the day and once or twice at night. There is no residual urine.

SUMMARY

A case of hypotonic neurogenic bladder due to intramedullary spinal cord disease was presented. After transurethral resection of the bladder neck and posterior urethra, the residual urine dropped from over 700 cc. to less

than 30 cc. Although voiding is mainly accomplished by the use of intra-abdominal pressure, he is able to empty his bladder and his pyuria has disappeared.

CONCLUSIONS

Neurogenic disturbances of the bladder are more readily diagnosed today with the increased knowledge of bladder neurophysiology.

Atonic neurogenic bladders with residual urine can be treated successfully by transurethral resection.

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DYNAMICS OF SYMPTOM PRODUCTION IN SPLENOMEGALY

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In a review of 250 cases in which splenomegaly was an outstanding feature, the occurrence of certain remote symptoms was more frequent than one would have expected from chance alone. In these patients, including examples of most of the common causes of splenomegaly, 75 per cent complained of general weakness; 58 per cent of dizziness, (probably giddiness rather than true dizziness); headache, 51 per cent; constipation, 35 per cent; pain in the left upper quadrant, 35 per cent; vomiting, 25 per cent; nausea, 35 per cent; cough, 25 per cent; palpitation, 25 per cent; feeling of fulness in the left upper quadrant, 25 per cent; abdominal discomfort, 22 per cent; dragging feeling in left upper quadrant, 21 per cent; mid-epigastric pain, 20 per cent; anorexia, 15 per cent; fever, 12 per cent; jaundice, 11 per cent; pain on deep inspiration, pain in left shoulder, pain in left side of the chest, symptomatology in the chest, but with a "negative" chest x-ray study, tender spleen and pain in the "back", each 10 per cent. Eight per cent of the patients showed one or more of the following: pain in the left leg, discomfort in certain positions, night sweats, hemorrhoids, chills, "buzzing in the ears". Of the following, one or more was present in six per cent of the individuals: pain in the right upper quadrant, diarrhea, cough, without extensive sputum production, gastrointestinal upsets, difficulty in bending, tenderness of the trapezius muscles, or dysphagia. A few patients (about 4 per cent) showed left otitis media, soreness of the inner surface of the left thigh, "tightness" of the left knee, productive cough, pain in the abdomen, worse after eating, swollen left testicle, tenderness of the left deltoid muscle, friction rub in the left axilla, pain in the left arm, visual disturbances, or the left pupil smaller than the right.

While many of these symptoms appeared to be related to the associated disease, and especially to anemia or myocardial insufficiency, the presence of the same symptom under the most diverse conditions suggested an underlying mechanism associated with the location and physiology of the spleen itself.

The location and innervation of the spleen are factors in symptom production when the organ is enlarged.

The normal spleen is suspended in the upper left corner of the abdomen, in contact with the diaphragm on its outer and upper surface, lateral to the region of the cardiac apex. It is suspended by filmy bands, attached to the

stomach, diaphragm and colon. When the spleen is enlarged, the adhesions to the diaphragm may become more extensive, involving the central as well as the lateral area of this organ. This feature is important in the production of certain symptoms. Occasionally the suspensory ligaments are stretched or elongated, and the spleen may descend, even into the pelvis.

The position of the enlarged spleen accounts for some symptoms. There may be a feeling of fullness after the ingestion of a small amount of food, and pressure on the colon and intestines may be factors in the production of constipation or diarrhea. The upward displacement of the diaphragm causes the cardiac apex to deviate to the axillary line, especially when the patient is lying down. The patient may be conscious of his heart beat; there may be precordial pounding or palpitation and occasionally dyspnea. There may be an actual limitation in the movement of the diaphragm, with reduction in the vital capacity. The displaced apex, with dyspnea and a hemic murmur from associated anemia, often leads to a diagnosis of a cardiac lesion.

A grossly enlarged spleen may cause congestion of the abdominal or leg vessels by direct pressure. This may result in pain in the left leg and edema.

The diagnosis of enlarged spleen is best made by direct percussion with the flat surface of the middle finger of the right hand. The skin is struck directly and the change in vibration in passing from the air containing lung to the duller area of the spleen is noted. Too great an area is set in vibration when the usual method of percussion is used (middle finger of the left hand in contact with the chest; finger of the right hand used as percussion hammer).

With the direct percussion, two types of individuals are noted. In one the reflection of the spleen on the body wall is 9 cm. in its greatest length, in the other it is 11 to 13 cm. It will be found that normally the former size is found in men with hairy chests, whereas the larger type is found in the so-called thymico-lymphatic type. The normal for one type is pathological for the other type.

It is probably not wise to "dig" for the spleen. When it is enlarged it can be detected by approaching the splenic area from the surrounding region, merely indenting the skin with the finger tips. The spleen occasionally appears to recede after it is palpated. This may be the result of changing its position or of contraction (possibly associated with a change in the blood content, the involuntary muscle fibers of the human spleen being mostly in the blood vessels).

The spleen may be enlarged to two or three times the normal volume and four times the average weight without being palpable. A palpable spleen is not always enlarged. It may be pushed down by a low diaphragm.

The innervation of the spleen is important from the point of view of

symptom production. While the spleen itself is insensible to pain stimuli, pain is often referred to this region. The sympathetic nerves of the spleen arise from the third to the tenth thoracic segments. The vascular innervation is from fibers from the third to the twelfth thoracic and the first to the fourth lumbar segments, through the semilunar (celiac) ganglion. Fibers from the vagus also enter the spleen (fig. 1).

These fibers constitute the intrinsic innervation of the spleen, but an additional group outside of the spleen are affected when the organ is enlarged. Through its attachment to the outer part of the diaphragm, the local intercostal nerves are involved. When the spleen enlarges, the central part of

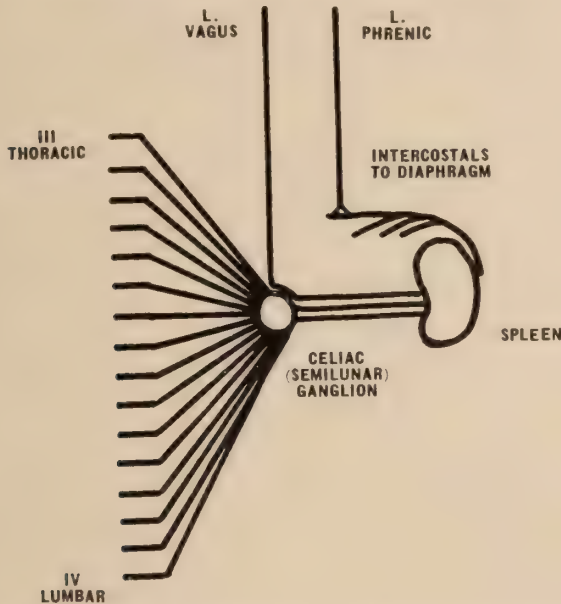


FIG. 1. Diagram of innervation of the spleen and diaphragm

the diaphragm, innervated by the phrenic nerve from the third, fourth and fifth cervical segments, is involved. Some of the fibers of the phrenic nerve run to the outer part of the diaphragm.

The symptoms which can arise from direct stimulation of the nerves or from "referred" or "reflex" action are many (Pottenger (4)).

When the spleen enlarges, the constant irritation of the segments of the spinal cord with which the nerves are associated, causes the other nerves from these regions to be "hypersensitive". Thus the intercostal nerves of the region register tenderness referred to the skin of the lower left part of the chest. Through the phrenic fibers, the cervical cord becomes sensitized, and the skin of the left shoulder and sternal region show tender points (fig. 2). There may be pain in the left shoulder, present in 25 pa-

tients in our series. In one patient, with chronic myelogenous leukemia, it was limited to an area about 2.5 cm. in diameter over the anterior surface of the deltoid. It was dull and continuous in character and not aggravated on motion of the shoulder joint. This pain was a source of great discomfort and repeated x-ray studies failed to show any bone or arthritic involvement. Local applications were ineffective, but the pain subsided upon reduction in the size of the spleen with x-ray therapy.

Areas of referred pain may be in the cervical region, over the trapezius muscle, in the epigastrium and in the lower costo-vertebral region posteriorly.

Through the vagus pathways, the nucleus of the vagus may become hypersensitive, as well as the associated nuclei (fifth nerve). Dizziness or giddiness may be a symptom (145 patients), as well as nausea (87 cases)



FIG. 2. Tender areas (shaded) in enlargement of the spleen with involvement of the diaphragm.

and vomiting (62 cases), headache (78 cases) and cough (63 cases). In these cases it had been assumed that the symptoms were secondary to some unknown feature of the underlying disease. In patients with anemia one would think of some chemical disturbance associated with an oxygen defect, but the presence of some of these symptoms in non-anemic individuals suggests the rôle of the "referred symptoms" on a basis of the type of innervation. Foerster was able to produce nausea and vomiting when he stimulated the central ends of the cut vagus, below the diaphragm.

While the basis of the symptoms of feeling of fullness in the left upper quadrant, pain and a dragging sensation in this region would at first seem self-evident, yet the absence of sensation in the spleen itself, and its total lack of pain when stimulated, suggests that these may be a referred basis for these sensations. Similarly 25 patients at some time in their disease showed enough symptoms attracting the attention to the chest, to have an x-ray examination, without, however, any positive lesions being found.

The acute pain associated with splenic hemorrhage or infarction is usually attributed to stretching of the capsule or to peritoneal involvement. The mechanism must be of a "referred" type, as is noted when there is skin tenderness over inflamed abdominal viscera.

A rather curious feature was the presence of otitis media in 10 individuals with splenomegaly, the ear involved being on the left side in each case. (Five other similar cases, not in this series, have been noted.) It is not known whether this was a chance occurrence, or whether it is secondary to changes in the nerves associated with the vagus. Alvarez (1) noted that when a surgeon accidentally injures one of the vagus trunks, the patient will feel pain in the skin about the ear, and he observed it in patients with gastric hemorrhage and in one with cholecystitis. Cases of this type are cited by Rasdolsky (2). Whether referred pain led to paracentesis, and this to otitis media, or whether there is some other relation, is not known.

Thus it is possible that many of the symptoms in patients with a large spleen may be of the "referred" type, associated with the nerves leading to and from the spleen and surrounding structures. The great variation in the conditions in the different patients may account for the different degrees of symptom production, from no symptoms to those of the most peculiar type. Some symptoms which have been attributed to the underlying disease may thus have their origin in the innervation of the spleen or its surrounding structures.

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AN EARLY CASE OF HORSESHOE KIDNEY (THOMAS BARTHOLINUS, 1659)

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The brief case report reproduced herewith is notable for the excellence of its illustration and for the engaging naiveté of its text. Moreover it also affords instructive retrospect toward those early days when pathological anatomists were occupied with the more obvious and impressive gross lesions, especially malformations.

The fine details of the illustration attract the reader's attention at once. Quite evidently the specimen was dissected with great care, each arterial and venous branch having been identified and followed to the end. A twentieth-century anatomist could have done no better.

The illustration depicts a familiar variety of horseshoe kidney. The two halves, not quite equal in size and shape, are joined at the lower pole by a mass of renal tissue situated immediately cephalad to the aortic bifurcation. The isthmus receives an arterial twig from the aorta and is drained by a small vein which enters the left iliac vein. The two renal pelves are separate and emerge ventrally.

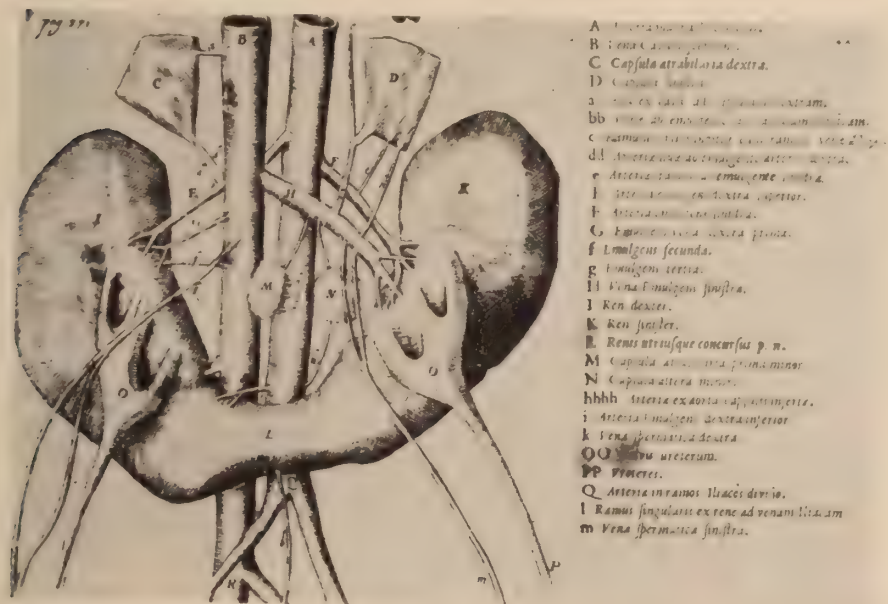
The structures marked M and N are called "Capsulae atrabiliariae minores", which can be translated "accessory adrenal glands". These may be lymph nodes or may represent chromaffin tissue similar to the so-called organs of Zuckerkandl (*Anat. Anz., Ergänzungsh* 19: 95-107, 1901).

This case report was originally published by Thomas Bartholinus in his *Historiarum Anatomicarum Centuriae*, printed at the Hague, 1659. The case and the illustration were published again in 1726 by Gerard Blasius in his revised edition of Lorenzo Bellini's book on the kidney. For those who may be interested to pursue the subject further I have added a brief list of publications dealing with early cases of renal anomaly.

UNUSUAL CONFORMATION OF THE KIDNEYS AND ATRABILIARY CAPSULES

I would not include woman among the monstrosities. Aristotle called woman an aberration of Nature. Others deny that women are human. All men who hold such opinions are unjust to the opposite sex. Yet Nature often plays tricks upon womankind, especially in the organs of gestation. In the cadaver of a woman of Padua dissected in 1643 we observed a rare conformation of the kidneys and atrabiliary capsules. The kidneys (I, K) on either side were situated in the customary place but had grown together (L)

above the iliac bifurcation (Q). The pelvis (O) of each ureter (P) was clearly visible beyond the kidney, and emerged in three parts. The atrabiliary capsules were four in number. The upper right capsule (C) was triangular, the left (D) was square; the two lower capsules (M, N) were round, globular, and unequal, and received arteries (h) from the trunk and veins from the emulgent vein (H). The number of emulgent veins was unusual. The right emulgent vein was triple (G, f, g) but small; that on the left (H) was thicker but split into three parts before entering the kidney. The right emulgent artery (E) was double, the left artery (F) was single but likewise divided before insertion. The right spermatic vein (k) arose from the main trunk, divided near the middle and united again. The left spermatic vein (m) arose



conspicuously by a double origin from the left emulgent vein (H). There were no spermatic arteries. A single branch (l) passed from the junction of the kidneys (L) downward to the iliac branch.

In order to show these things more clearly, I have decided to place the details before your eyes in the accompanying picture.

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THE NEURO-PSYCHIATRIC MANIFESTATIONS OF VITAMIN DEFICIENCIES*

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It is now accepted that normal functioning of the nervous system is dependent, among other things, upon: 1) An adequate carbohydrate substrate; 2) An adequate supply of oxygen; and 3) Intact enzyme and co-enzyme systems.

It is known that a deficiency of any of these essential factors may lead directly or indirectly to a neuro-psychiatric disorder. The mental confusion in hypoglycemia, progressing to excitement, stupor, coma and convulsions, is a well known syndrome caused by disturbances in the carbohydrate substrate. The mental confusion in anoxemia, whether induced experimentally or by high altitude, anemia, or heart disease, is also a well known result of oxygen deficiency. The psychoses of pellagra and the polyneuropathy of beriberi are classic examples of deficiencies in enzyme and co-enzyme systems.

During the past decade vitamin deficiency has often been looked for and nearly as often found in many neuro-psychiatric disorders. It must be emphasized, however, that the mere finding of a vitamin deficiency concurrent with a disease does not indicate that this deficiency is the cause of the original disease. Secondary or "conditioned" vitamin deficiencies should be clearly distinguished from the original or primary disease, otherwise utter confusion will result. It is probable that secondary deficiencies constitute a larger problem in neuro-psychiatry than primary deficiencies.

Almost every vitamin has been credited with a role in the maintenance of a normal nervous system. The more important of these are thiamin, nicotinic acid, riboflavin, pyridoxine, and alpha-tocopherol, yet only thiamin and nicotinic acid have been related clinically in a definite causal role to neuro-psychiatric syndromes in man.

THIAMIN DEFICIENCY

Deficiency of thiamin leads progressively to a neurasthenic syndrome, then to involvement of the peripheral nerves and spinal cord, and finally to involvement of the midbrain and neighboring structures. The human

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requirement of vitamin B₁ has been gauged by the minimal amount necessary to prevent polyneuropathy. Compared to the requirement of the peripheral nerves it is probable that larger amounts of thiamin are necessary to prevent a neurasthenic syndrome while smaller amounts are probably sufficient to maintain normal function of the midbrain nuclei.

The experimental production of isolated thiamin deficiency in human subjects indicates that a neurasthenic syndrome is the earliest evidence of thiamin deficiency in man. The work of Williams, Mason, Wilder, and Smith (1) at the Mayo Clinic, who confirmed and extended the work of Jolliffe, Goodhart, Gennis and Cline (2) at Bellevue Hospital, indicates that thiamin deficiency is one of the factors capable of producing a neurasthenic syndrome in susceptible individuals.

For several years I have been cognizant of neurasthenia in patients having the objective signs of vitamin B₁ deficiency. I have usually attributed the neurasthenic symptoms to an abnormal psyche which, leading to further dietary restrictions, resulted finally in the development of the objective signs. I still believe this to be the course in many such patients. However, adequate treatment of the deficiency was followed in certain instances not only by disappearance of the objective signs but also, of the neurasthenic syndrome. I then applied the therapeutic regimen of dietary correction with vitamin supplements rich in the entire B-complex and thiamin hydrochloride to patients having the neurasthenic syndrome without objective signs of vitamin deficiency. Many of these patients were helped. The improvement was attributed at first to better nutrition plus the psychotherapy of such a regimen. Not until Williams et al. (1) reproduced the characteristic neurasthenic syndrome in a well-controlled experiment of induced isolated thiamin deficiency in normal human subjects have I been willing to consider it a direct manifestation of vitamin B₁ deficiency. It should not be inferred, however, that all neurasthenia is based on thiamin deficiency. Such is definitely not the case. Almost any agent causing the triad of anorexia, fatigue, and disturbances of sleep, if not relieved, will, in susceptible persons, further the development of other neurasthenic symptoms. Nevertheless, the incidence of neurasthenia caused by vitamin deficiency may be larger than is now commonly believed.

Pathological alterations in the peripheral nerves have been more generally accepted as manifestations of thiamin deficiency. At first only the polyneuropathy of beriberi was proved to be a vitamin B₁ deficiency and was believed to be rare in the Western world. Then in succession many of the symmetrical polyneuropathies often seen in this country and in Europe were proved to be due to a nutritional deficiency similar in every way to that underlying the polyneuropathy of Oriental beriberi. These polyneuropathies occur in association with alcoholism, pregnancy, cachexia, pellagra, hyperthyroidism, chronic gastrointestinal dysfunction, diabetes, and postoperative nutritional disturbances. Almost all authorities concur

in this viewpoint. There is some disagreement (3), however, as to whether thiamin deficiency alone will produce a polyneuropathy in man, or whether a deficiency of some other vitamin must exist as well. The latter point of view has recently received support in the work of Williams et al. who were unable to produce unequivocal objective evidence of polyneuropathy in a group of six women. These subjects were maintained at room rest, with diets deficient in thiamin only (containing 50 I.U. per day) for a period of 88 days. In addition to a neurasthenic syndrome some of these subjects developed such symptoms as burning of the soles of the feet and numbness of the legs, and such signs as calf muscle tenderness and depressed tendon reflexes. This evidence is suggestive, but not proof, of peripheral nerve involvement. It is possible, however, that had these women been placed under metabolic strain these signs suggestive of polyneuropathy would have developed into definite ones.

The fact that diets deficient in thiamin are almost certainly deficient in other fractions of the vitamin B-complex has been used as an argument against the thiamin-deficiency genesis of nutritional polyneuropathy. The mere fact, however, that other B-vitamin deficiencies may be coincidentally latent or even manifest does not negate the close, consistent parallelism between thiamin deficiency and polyneuropathy. Many patients having pellagra have associated polyneuropathy. The stomatitis of this disease may be dramatically cured by nicotinic acid while the polyneuropathy remains unchanged. Conversely, the polyneuropathy may be improved by thiamin and the stomatitis remain unimproved. We (4) have studied several subjects having simultaneous deficiencies of thiamin, riboflavin, and nicotinic acid. When the patients were maintained on a basal diet inadequate in the entire vitamin B-complex, the specific clinical signs of each deficiency could be made to disappear separately by administration of the indicated specific vitamin. It is important to point out, however, that the patients were not cured completely until the entire vitamin B-complex and a good diet had been administered.

The clinical picture of "nutritional" polyneuropathy, although somewhat varied, is almost always preceded by a neurasthenic syndrome. Neurologic examination during the neurasthenic stage discloses, as a rule, no abnormal signs. Soon, however, plantar hyperesthesia and calf muscle tenderness develop, both significant objective signs. The plantar hyperesthesia is not the ordinary tickling sensation usually elicited by scratching the plantar surface of the foot, but a definite hyperesthetic pain which is manifest and unmistakable in the facial expression. The healthy calf muscle, if squeezed from behind so as not to include the tibia in the grip, can tolerate considerable pressure before pain is felt; this is not so in the presence of mild vitamin B₁ deficiency. At about this time, too, vibratory sensation in the toes becomes diminished. These signs, however, are only suggestive. A positive diagnosis of polyneuropathy cannot be made

from them alone, since circulatory disturbances of varying etiology may cause these or similar findings (5). However, when, in addition to these signs, the ankle jerks are absent, a diagnosis of mild polyneuropathy should be made. By this time the plantar hyperesthesia may have extended so that there is "sock dysesthesia." Vibratory sensation is usually absent in the toes at this stage, and occasionally may be absent in the malleoli or even in the tibiae. Position sense, as a rule, is intact in the toes, although a few mistakes may be made in very small changes in position.

As the deficiency progresses to the development of moderate polyneuropathy, knee and ankle jerks can no longer be elicited, but positive signs are still limited to the lower extremities. Impairment of position sense in the toes is now generally definite, and vibratory sensation is lost over a greater area than before, occasionally even up to and including the pelvis. Some atrophy of the calf muscles may be evident. Calf tenderness and "sock dysesthesia" persist. Occasionally "delayed" plantar hyperesthesia exists. Toe drop or foot drop is not often present at this stage. The gait may be natural, but often a definite abnormality is noted. The burning sensation in the soles of the feet with diminished position sense may compel these patients to walk carefully as if barefoot on a floor strewn with tacks.

If the deficiency continues, the upper extremities become involved so that the biceps and triceps jerks disappear. "Glove dysesthesia" and loss of finger dexterity rapidly develop. Calf muscle atrophy is now usually marked, toe drop and foot drop are also plainly evident, and wrist drop soon appears. The gait, if the patient is able to walk, is by now of the steppage type. Walking, however, is as a rule impossible because of involvement of the central nervous system or circulatory system.

The neurologic manifestations of vitamin B₁ deficiency, whether in mild or severe degree, are bilateral and symmetrical, and characteristically involve first and predominantly the lower extremities. Peripheral neuritis that involves a single nerve, or that is not bilateral and symmetrical, or that does not involve first and predominantly the lower extremities, is not, in my experience, due primarily to vitamin B₁ deficiency. Exceptions can probably be found for each of these statements. For example, a case may be cited of a man crippled by hip joint disease who was confined to a wheel chair which he propelled with his arms. Polyneuropathy occurred first and predominantly in his upper extremities.

Any time during the course of the polyneuropathy signs of midbrain involvement may appear, such as ophthalmoplegia. These signs, in our (6) experience with 30 cases, never appear in the absence of polyneuropathy. They are usually precipitated by a period of delirium, diarrhea, vomiting or fever. These precipitating factors, it should be noted, are factors which simultaneously increase the vitamin requirement, or pre-

vent its absorption from the gastrointestinal tract. In addition to polyneuropathy and ophthalmoplegia these patients usually present clouding of consciousness and ataxia, making possible the clinical diagnosis of Wernicke's disease. In general, the pathologic change is confined to the periventricular gray matter and is characterized by foci of degeneration and varicose deformities of the blood vessels. Most of the cases reported occurred in association with alcoholism. A significant number, however, have been reported (7) in non-alcoholics, particularly in association with vomiting, cachexia and severe gastrointestinal disease.

Experimentally, Alexander (8) produced in pigeons, made deficient in thiamin, brain lesions similar to those found in man. He was unable to produce this lesion in pigeons receiving thiamin, but deficient in other vitamins.

We (6) have studied 30 cases of Wernicke's disease, three of which were in non-alcoholics. From these studies we have shown that the ophthalmoplegia of Wernicke's disease is due to a deficiency of, and responds to, thiamin. The clouding of consciousness also responds to thiamin in some instances, but not to nicotinic acid. At other times it responds to nicotinic acid, but not to thiamin. On still other occasions it will respond to large doses of the entire vitamin B-complex, but not to nicotinic acid and thiamin. In some cases it is apparently irreversible. It is thus obvious that in Wernicke's disease two or more vitamins (thiamin and nicotinic acid) may play a role. Although we are unable to designate the additional vitamin or vitamins involved in such cases, we believe the common source will eventually be found in the B-complex. It is suggested that each patient should be carefully observed for clinical signs, and his response to specific vitamins recorded; in fatal cases the pathological changes should be correlated with the clinical picture. Only by careful observation will the role of thiamin and the other vitamins in encephalopathies be determined.

NICOTINIC ACID DEFICIENCY

The role of nicotinic acid in the maintenance of normal function of the nervous system has been known since Elvehjem, Madden, Strong and Woolley (9) proved nicotinic acid to be the factor necessary for the cure and prevention of blacktongue in dogs, the experimental analogue of human pellagra. These results, reported in 1937, stimulated various workers to use nicotinic acid in the treatment of human pellagra. Three groups (10) reported the efficacy of nicotinic acid in human pellagra in November and December of 1937. Following this, it was quickly discovered that pellagra was a multiple vitamin deficiency. Its characteristic polyneuropathy was proved to be vitamin B₁ deficiency (11). The cheilosis and certain other characteristic lesions of the face (4) and of the cornea (12) proved to be riboflavin deficiency. Some of the mental

symptoms (13), mouth and other mucous membrane lesions, have been proved to be nicotinic acid deficiency. The bilateral dermatitis has been shown to be nicotinic acid deficiency conditioned in some way by trauma. As in thiamin deficiency, objective signs of nicotinic acid deficiency are often preceded by psychoneurotic symptoms. This is true for both spontaneous and experimental human pellagra, as shown by McLester, by Sydenstricker, and by Spies et al. (13). These symptoms, as described by Frostig and Spies (14), were proved to be fairly uniform and, according to these investigators, had no connection with the underlying personality. These symptoms included hyperesthesia involving all forms of sensation, increased psychomotor activity, definite trends toward depression and apprehension, and weariness, fatigability, headaches and insomnia.

Following the development of classic pellagra the mental symptoms commonly seen are those found in any organic psychosis. These include memory defects, disorientation, confusion and confabulation. Periods of excitement, depression, mania, delirium, and paranoia occur not infrequently. These mental disorders may appear before other signs of pellagra are evident. Response to nicotinic acid is usually prompt, especially when the psychosis is of short duration. In the psychoses of longer duration the response is often by no means so spectacular, and frequently specific therapy does not help at all. This may mean that in the latter cases the process has advanced to an irreversible stage. It must be emphasized, however, that pellagrins lack other dietary factors necessary for normal brain metabolism, and these deficiencies may contribute to the cerebral manifestations. Adequate amounts of all other nutritive essentials should therefore be given in order to obtain a maximal therapeutic response.

We (15) have recently described a fairly characteristic neuropsychiatric syndrome which we have labeled Nicotinic Acid Deficiency Encephalopathy. This syndrome may occur as the only clinical manifestation of a deficiency disease or it may occur in association with pellagra, polyneuropathy, scurvy or ariboflavinosis. The clinical picture of the encephalopathic syndrome is characterized by clouding of consciousness, cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. Patients manifesting this syndrome treated only by hydration or hydration plus thiamin hydrochloride almost invariably died (95 per cent); patients treated by hydration plus concentrates rich in the vitamin B-complex showed a significant drop in mortality (50 per cent); but when these patients were treated by hydration plus nicotinic acid the mortality fell to 15 per cent.

The fact that only about half of our 150 subjects having this syndrome presented other signs of nicotinic acid deficiency, and the fact that in endemic pellagra the encephalopathic syndrome occurs only in the most advanced and severe cases, does not necessarily controvert the evidence that this syndrome is a manifestation of nicotinic acid deficiency. The

encephalopathic syndrome represents, in our opinion, a complete acute nicotinic acid deficiency, while the pellagral syndrome (stomatitis, mental symptoms, diarrhea, dermatitis) represents a chronic partial deficiency of nicotinic acid not complete enough to produce the encephalopathic syndrome. If this is so, patients having both clinical pellagra and the encephalopathic syndrome represent chronic, partial deficiency of nicotinic acid of sufficient duration to produce the structural changes recognizable as pellagra, upon which has been superimposed a complete nicotinic acid deficiency; patients showing the encephalopathic syndrome without signs of pellagra represent on the other hand a complete nicotinic acid deficiency which develops so rapidly that the characteristic structural changes in the mouth and skin do not have time to develop.

A relationship of thiamin, nicotinic acid, and ascorbic acid to infantile paralysis, delirium tremens, or Korsakoff's psychosis has been suggested but, in my opinion, not proved. In all these, as in many other diseases, an associated or secondary vitamin deficiency may occur. In delirium tremens the marked increase in total metabolism raises the vitamin requirement to such an extent that an acute deficiency may be precipitated from which the patient may die unless adequate nutrition is insured.

OTHER VITAMINS

The value of alpha-tocopherol and of pyridoxine in the syndromes of muscular dystrophy, amyotrophic lateral sclerosis and paralysis agitans has recently been the subject of conflicting reports (16). In all disorders which may be viewed as syndromes rather than as disease entities a positive response to treatment in even a few patients is significant, for it may indicate a curable disease entity within a syndrome previously considered irreversible. It seems reasonable, therefore, in view of the conflicting reports and of the progressive nature of these syndromes, to administer the vitamins on an experimental basis, under carefully controlled conditions.

Syndromes collectively labeled paralysis agitans, while not directly fatal, usually follow a progressive course, and the victims eventually become helpless. Since muscular rigidity and weakness is characteristic of paralysis agitans, and since pyridoxine (vitamin B₆) is involved in muscle metabolism, it seemed worth while to test its effect in this syndrome. In the Spring of 1940 I reported (17) the treatment of 15 patients having paralysis agitans with 50 or 100 mg. of pyridoxine parenterally either daily or every other day for at least 4 weeks. All these patients were chairfast or bedfast, 10 for more than 3 years. Of these 15 patients 4 showed definite objective improvement. Similar results were reported a short time later by Spies, Hightower and Hubbard (18), and Baker (19) has recently confirmed the beneficial effects of vitamin B₆ in Parkinsonism.

Of our four patients who showed objective improvement two have since

died, one following fracture of the femur and the other following myocardial infarction; the improvement in these two patients had been maintained until the onset of the terminal illness. The improvement in the third patient has now been maintained for over 16 months (July 1941) although he must receive pyridoxine parenterally three times a week, for which saline, thiamin or nicotinamide cannot be substituted. The fourth patient has regressed so that now the tremors and rigidities are about the same as they were at the start of the treatment.

In our report of these 15 helpless patients it was stated: "Thus far objective beneficial results . . . have been limited to the lessening of rigidities and increase in strength in patients whose complete disability was of less than three years' duration." One of my associates (20) has studied 12 cases of long-standing Parkinsonism (average duration $10\frac{1}{2}$ years) and noted no beneficial results from adequate pyridoxine therapy. Since then

TABLE 1
Ambulatory patients with paralysis agitans
Pyridoxine treatment of three weeks or more

GROUP	NUMBER	IMPROVEMENT				CONTINUING THERAPY
		None	Subjective	Objective	Return to work	
Arterioscl.....	6	5	1	0	0	1
Post-enceph.....	10	4	6	4	2	6
Idiopathic.....	16	10	6	2	1	7
Total	32	19	13	6	3	14

46 ambulatory patients having paralysis agitans, without selection according to age, type, or degree of disability, have been treated with pyridoxine. Fourteen patients, all of whom showed no improvement, abandoned the treatment in less than 3 weeks. Shorter trials of therapy, as the administration of "daily doses of 50 to 100 mg." (repeated only 1 to 3 times) recently reported by Zeligs (21), are inadequate for judging this form of therapy. Of the remaining group of 32 patients who continued the treatment longer than 3 weeks, 23 were economic cripples. In this group worth while results were shown (Table 1). The most conservative estimate of improvement would be to take as a criterion the 10 per cent who showed economic rehabilitation (one as a farm hand, one as a clerk in a vegetable market, the third as an insurance broker). A less conservative estimate would be the 20 per cent who showed objective improvement. A far too liberal estimate would be the 40 per cent who show subjective improvement such as seen in the thirteen who are still willing to continue treatment that involves travel and the discomfort of injections.

The fact that the improvement in helpless patients first reported was

limited to the idiopathic and arteriosclerotic types, while in the ambulatory series reported later (22) improvement seemed more frequent in the post-encephalitic group, indicates that the entire series is still too small to allow definite conclusions to be drawn. It seems justified to say, however, that the syndrome of paralysis agitans, if not of too long duration, appears to include persons who are helped by pyridoxine.

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MECHANISM OF HEART FAILURE¹

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One of the primary problems connected with the activity of the heart is that concerning failure. Much has been written on this subject and polemics in this field are rife. During the course of years I have had many occasions to consider the clinical and experimental aspects of this subject. More recently my associates and I became interested in this problem and investigated it on an analytical basis in the animal laboratory. As a result of these considerations and this experimentation, it soon became evident that some of the controversy and misunderstanding of this subject was due to a poorly defined terminology. One of our first tasks, therefore, in considering the subject is to clearly define the various terms employed. Having done that, we can try to reconstruct the background of the mechanism of heart failure.

The fundamental elements of the physiology of the circulation. Before we can deal adequately with this subject, it is worthwhile to present in its simplest terms, the functional constitution of the circulatory system. In figure 1 are shown the elements of the circulatory tree with its two major pumps, the right ventricle (RV) and the more powerful left ventricle (LV), together with their antechambers, the left (LA) and right (RA) auricles, which accommodate the blood going to these pumps, and the A-V and semilunar valves which help to direct the motion of blood forward. Interposed between the right and left hearts is the pulmonary circuit with its pulmonary artery, intrapulmonary arteries, arterioles, capillaries, venules and veins (represented in figure 1 by the network L), and the large pulmonary veins. The blood from the left ventricle passes out through the main conduit, the aorta (A), from which it is distributed throughout the body to all the organs by a network of arteries, arterioles, capillaries, arteriovenous anastomoses, venules and veins (represented in figure 1 by the network P). The blood is again collected into the conduits composed of large veins (V) and returned to the right heart.

It is the pumps which keep the blood in motion, and impart an increased pressure to it as it leaves the heart in order to create that pressure gradient which is essential for the onward movement of the blood. The develop-

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ment of the continuous motion of blood in the peripheral network in the systemic and pulmonary parenchyma depends upon the pulmonary artery and the aorta and their major subsidiary branches which constitute the elastic reservoirs of the circulation. By virtue of their elasticity, the elastic reservoirs take up part of the output of the ventricles during systole and expel it into the periphery during diastole.

Not all of the blood in the body is in active circulation. Some of it is stored in various blood reservoirs, the most important of which are those of the skin, the lungs and that of the splanchno-hepatic circuit. Variations in the capacity of these blood reservoirs alter the quantity of the blood in active circulation to suit the changing circumstances. This variable capacity of the blood reservoirs is of importance in adjusting the output of the heart to the needs for circulation to the tissues.

While all parts of the circulation are under the control of the autonomic

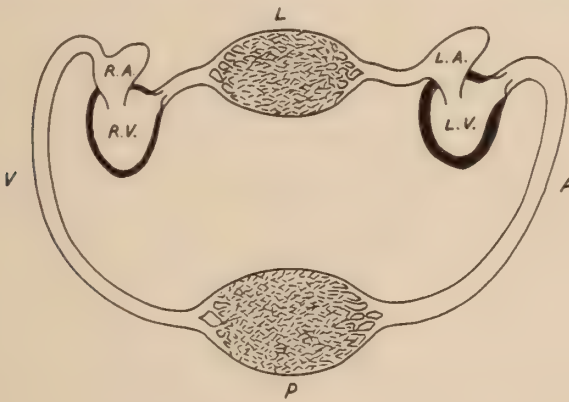


FIG. 1. Diagram of the circulatory tree. Discussed in text

nerves to varying extents and respond reflexly in their adjustments for immediate needs, and while they are also subject to the influence of various hormones and other chemical substances circulating in the blood, the most important adjustment is by the operation of Starling's Law of the Heart. In essence, this law states that the heart, by changing its diastolic size, automatically adjusts its output to take care of the venous blood returning to it. This implies that the venous return to the heart is the key to the major mechanism adapting the heart's output to the circulatory needs of the body. It is one of the important homeostatic properties of living organisms.

In a consideration of venous return, the valves located in the veins are essential because their presence permits all fluctuations in pressure on the venous side to be translated into flow toward the heart. Such variations in pressure accompany muscular activity, whether it be movements of the skeletal muscles, of the smooth muscles of the gut, or the intermittent

pumping action of respiration. In this same category falls the miniature contractions that represent neuromuscular tone in skeletal muscles which, together with bodily sway, are of vital importance in overcoming the action of the gravity in such upright creatures as man. Aside from this, of course, the venous return depends upon the pressure gradient existing between the pressure in the capillaries and the negative pressure (with respect to the atmosphere) in the intrathoracic cage. The former is the pressure remaining in the blood after the loss of energy in overcoming the resistance encountered in traversing the arterial tree and the capillaries.

Circulatory failure. With this summary in mind, we are prepared to consider and define circulatory failure and differentiate it from heart failure. Circulatory failure may be defined as an inadequacy in the amount of blood passing through the capillaries in the tissues. This is not equivalent to heart failure because such circulatory failure may also arise when the volume of blood in circulation is insufficient to fill the circulatory tree. This may occur by a reduction in the actual volume of the blood in circulation as in hemorrhage or in shock, or by an increase in the capacity of the circulatory tree without a concomitant proportional increase in the total blood content as occurs when the peripheral blood vessels are markedly dilated in peripheral circulatory collapse. Under both of these circumstances the circulatory failure is not the result of a primary defect in the cardiac pumping mechanism but is secondary to the decrease in the venous return to the heart with a consequent reduction in cardiac output. One should, therefore, sharply distinguish between primary failure of the heart and failure of the circulation.

Obviously, by definition, circulatory failure depends not only upon the rapidity of blood circulation but also upon the needs for blood at the time. Although the rate of circulation may be adequate for conditions of rest or for those under so-called basal conditions it may become inadequate when the bodily activity is increased as in exercise or in the increased metabolism which occurs, for example, in hyperthyroidism.

The integration of the pumping of the two ventricles with each other. The next major consideration in developing our concept of heart failure is the integration of the two pumps. Under ordinary circumstances the outputs of the two pumps are equal. This is also true under stabilized conditions when circulatory failure is present, or in the presence of a decreased pumping power of either the right or left ventricle. Since at each stroke, each ventricle expels about 60 cc. of blood and this occurs approximately 80 times a minute, any disparity in the output of the two pumps will quickly cause a depletion of blood in either the systemic or pulmonary circuits with congestion in the other, and death will quickly ensue unless the output of the two ventricles again becomes equal.

Let us assume, to make this point clear, that at each stroke, the right ventricle pumps out 1 cc. more than the left ventricle. At 80 strokes per

minute this will mean a depletion of 80 cc. from the systemic circuit and the addition of this amount to the pulmonary circuit in one minute. Now, the total amount of blood in the body can be assumed to be in the neighborhood of 7 per cent of the body weight which in a 70 kilo. man would amount to 5 liters. Thus, if the disparity between the outputs of the two ventricles continues unchanged, in one hour all the 5 liters of blood would be collected in the pulmonary circuit, and the systemic circuit would be empty. This is, of course, an extreme situation, but it serves to illustrate the point. It follows from this, therefore, that whether heart failure is present or not, the outputs of the two ventricles over any extended period of time are the same. Heart failure is, therefore, not a disparity in the outputs of the two pumps. This, I feel, is one of the prevalent misconceptions which leads to loose thinking about the problem of heart failure. Only when heart failure is developing or disappearing or when a person is dying because of failure of the heart, will such a disparity be present. Otherwise, the outputs of the two pumps remain the same over any extended period of time.

This might be thought of in terms of a river with two dams on it, one below the other. When the sluices are set so that the flows in the two dams are equal, the level of the water in the intervening portion of the river remains constant. However, when the upper dam allows a greater flow of water than is permitted by the lower dam, the level of the intervening stretch of the river rises until it overflows. On the other hand, when the lower dam allows a greater flow than the upper, the level in the intervening stretch will fall and this again may lead to undesirable consequences.

Of course, there exist here, as in the case of the circulation, certain hydrostatic factors which aid in establishing an equilibrium.

The heart as a machine. In pumping blood the heart does work. This work is, in part, the development of energy of motion (kinetic energy) imposed upon the blood leaving the heart. When we know the amount of blood ejected and the added velocity imparted to it we can measure this energy in foot-pounds or kilogram-meters. This energy of motion, however, is very small compared to the other form of energy, the energy of pressure (potential energy) also measured in foot-pounds or kilogram-meters, and calculated from the amount of blood put out by the heart and the added pressure imparted to it.

In order to do this work the heart, like any machine—for the heart is a machine—requires energy, and this energy comes from the breakdown of food stores in its muscles. Since these food stores are limited, they must be continuously replaced if the heart is to continue to do its work. It does this by resynthesizing some of the breakdown products released while it is working, the ultimate energy source for this replacement being the energy achieved through oxidation of its organic constituents.

From the time life first appears in the embryo the heart works con-

tinuously until death ensues. But the heart's work is done intermittently with periods of rest between. About one-third of the time it is in systole, breaking down its energy stores for the work that it has to do. The remaining two-thirds of the time it is in diastole, during which it restores the energy sources. It is obvious that if the heart is to maintain its power to beat, the restoration of energy stores during diastole must keep pace with their dissipation during systole. Were the breakdown ever so little greater than restoration, the heart would soon be choked up with the breakdown products and would soon deplete the sources from which it derives its energy. Unlike skeletal muscles which have a sizable credit and can develop a sizable obligation which we call oxygen debt, the credit of the heart is very poor. Its oxygen debt is low. We may again apply our example of the river and assume that the upper dam is set at a maximum rate of inflow while the lower dam may be opened to allow the intervening strip to be emptied of its fluid. In the case of skeletal muscle the level, i.e., the amount of material that can be drawn upon is high, while in the case of heart muscle it is low. It is nevertheless amazing how the heart can vary its work to a large extent under ordinary circumstances and maintain its energy equilibrium.

Unlike the steam engine the heart does not work by releasing heat. As far as the heart is concerned heat is a waste product. But like all machines the efficiency of the heart can be assayed by determining the ratio of work done to the amount of its stored energy which is converted into work. The ratio of the work accomplished over the energy liberated during its contraction gives the measure of its mechanical efficiency. This efficiency, computation has shown, is of the order of 25 to 30 per cent under the best physiological circumstances. Since the ultimate source of energy is primarily an oxidation reaction, the energy cost of the work of the heart can be determined from the oxygen it consumes. In such calculations, it has been customary to use the respiratory quotient of the heart, which has been found to be about 0.82, and to calculate from this the energy equivalent of the oxygen used. On the basis of these calculations it has been estimated that the heart would release about 2,000 kilogram-meters of energy per liter of oxygen consumed. While these figures presuppose that the energy obtained from the fuel is constant under varying circumstances, and this obviously may not be the case, nevertheless, the errors introduced by this assumption do not significantly alter the calculation even when heart failure develops.

The load of the heart and the cardiac adjustment to it. To further complete our analysis, we must point out that the heart works under a load and this load can be subdivided into three categories: 1) The resistance against which the heart empties its blood, namely the cyclic or mean pressure existing in the aorta and the pulmonary artery (the resistance-load). 2) The pressure head in its ante-chambers, the auricles, which determine its

filling (the input-load). 3) Hidden loads due to stenosis of valves, atresias in the aorta or pulmonary artery, valvular leakage, and congenital or acquired short circuits between the heart chambers.

The pressure head for filling, the input-load, can change either because the rate at which blood is coming to the heart is modified or because the volume of the circulating blood is altered. It may also change because the rate at which blood is pumped out by the heart is altered by modifications in the power of the heart. Actually a dynamic balance is established between these several factors.

The resistance-load of the left heart will change in amount only when the buffer nerve mechanism which tends to keep the systemic arterial pressure constant cannot cope with the forces tending to vary the resistance-load. The factors which alter the resistance-load are changes in the caliber and configuration of the peripheral blood vessels, variations in the properties of the elastic reservoir, variations in the amount of blood in the arterial tree, and alterations in the rate at which the heart is ejecting blood. These same factors operate upon the resistance-load of the right heart except that their effect is not buffered to any appreciable extent by the buffer nerve mechanism. In reality the most important mechanism varying the resistance-load of the right heart is the relative pumping power of the right and left ventricles.

In estimating the hidden loads it is imperative to recognize that the acoustic evidence is not always necessarily proportional to the dynamic significance of these loads, a fact not sufficiently appreciated clinically.

The heart must adjust its work to these loads in order that it may maintain an adequate circulation of blood. The heart has three methods by which it can meet the increase in load. First it can increase in size and by this means increase the available energy released for its work. Secondly, it can increase the number of its strokes per minute thereby enhancing the energy available for its work. Finally, it can, if given sufficient time, develop cardiac hypertrophy thereby permitting an increase in the numbers of "chemical factories" available to release energy.

While increasing the load of the heart leads to an increase in energy liberation and work done, the mechanical efficiency, the ratio between the two, varies depending on whether the input- or resistance-load is increased. It has been shown that the mechanical efficiency of the heart tends to improve when the input-load is increased but tends to decrease when the resistance-load is augmented. It is not difficult to understand why the mechanical efficiency would alter in different fashions under these two circumstances since the manner in which the heart does its work in these two conditions of increased load would be different.

The maximum work capacity of the heart and cardiac reserve. There is a limit to the increase in energy available for work which can be produced when the load is increased. Thus, if the load increases progressively, a

point will be reached when the heart can no longer cope with the existing load. This is the maximum work capacity of the heart. When the maximum work capacity of the heart is exceeded by the load a vicious cycle is established which leads ultimately to death unless the load is decreased. This ceiling placed upon the work capacity of the heart is due to the limitation in adjustment of each of the three compensatory mechanisms.

It is obvious that on increasing the heart size a point is eventually reached in which further increase in heart size is actually associated with a decreasing energy exchange. There is thus an upper limit to the operation of Starling's Law. This might be considered the point differentiating the dilated heart from the over-dilated one and it is in this sense only that the term "over-dilation" should be used. The value of the pericardium in preventing the attainment of this critical heart size in acute dilatation is apparent.

There is also a limit to the increase in release of energy which accompanies increase in heart rate. As the heart speeds up, a point is soon reached at which the quantity of energy released actually decreases. Furthermore, above a certain heart rate the coronary blood supply also becomes inadequate and leads to a reduction in the rate of recovery. The heart cannot fill so well as it speeds up, because the isometric relaxation phase of diastole, when no filling occurs, does not abbreviate nearly as much as the filling phases of diastole. In addition, it has been shown that with increased heart rate, the mechanical efficiency begins to decline so that the amount of work which can be obtained from the energy released decreases. The point at which further increases in heart rate give a decrease in the work of the heart is the second limit which determines the maximum work capacity of the heart.

Cardiac hypertrophy also reaches a point of diminishing returns because the number of the capillaries in the myocardium does not increase. This leads to an increase in the sectional area of muscle supplied by each capillary as the heart hypertrophies, and greater and greater parts of the heart muscle labor without an adequate blood supply. This is the third upper limit on the work capacity of the heart.

We are now prepared to discuss cardiac reserve. Cardiac reserve is the difference between the work the heart is doing and the maximum capacity for work that it is capable of doing. The first two columns of figure 2 show an attempt to illustrate this in the normal heart. The top of the columns give the maximum work capacity of the normal heart when the compensatory mechanisms of increased heart rate, increased heart size and cardiac hypertrophy are brought in to their optimum point. The top of the solid part of the column on the left shows the work output of the heart when the person is at rest. The difference between this level and the top of the column represents the amount of work the heart is capable of doing over and above that being done at rest. This is its cardiac reserve. As can

be seen in the next column, the cardiac reserve is reduced when the work of the heart is increased as occurs under normal bodily activity. In short, the cardiac reserve is the difference between the maximum capacity of work output of the heart and the work it is already doing. Increasing loads decrease the cardiac reserve by encroaching upon the total work capacity. This simple concept of cardiac reserve places on a semi-quantitative basis the more nebulous concepts which have been prevalent in the literature.

A decrease in cardiac reserve can also be produced by a decrease in its maximum work capacity such as occurs in disease of the heart. This is shown by the two columns on the right of figure 2, respectively, for resting

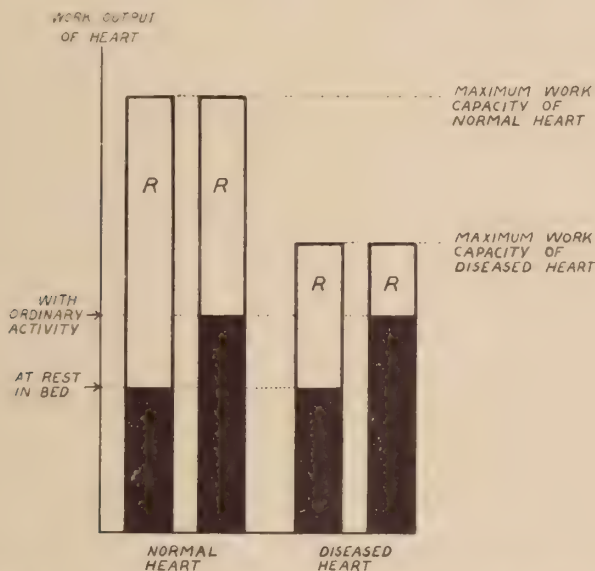


FIG. 2. Diagram showing the factors determining cardiac reserve in the normal and diseased heart. Discussed in text.

and normal activity in a patient with heart disease. Because the maximum work capacity is decreased in the diseased heart, the maximum load that can be placed upon it is less and the cardiac reserve at a given load is decreased below the normal. The degree of this decrease in maximum work capacity in heart disease may vary from an insignificant one to one in which only the strictest bed rest can be tolerated.

Whenever the load on the heart begins to approach its maximal work capacity clinical symptoms and signs such as fatigue, pain, dyspnea and congestion become manifest and, when properly evaluated to rule out other causes, they can be used to estimate the diminution in cardiac reserve. The importance of decreasing the load on the heart so as not to encroach upon the diminished cardiac work capacity in heart disease is thus apparent

and it is the background for the relief of symptoms and signs which follow the institution of measures to reduce the burden on the impaired heart.

Disease of the heart not only can cause a decrease in the maximum work capacity of the heart, but it also can increase the load on the heart by producing valvular defects, congenital or acquired shunts between the chambers of the heart, atresias of the exit chambers, arterial hypertension in the systemic or pulmonary circuits, or an increase in the venous return as in hyperthyroid disease, severe anemia and arteriovenous aneurysms. The decrease in cardiac reserve brought about by disease occurs, therefore, for two reasons: 1) The maximum work capacity of the heart is decreased and/or 2), the load on the heart is increased.

The contractile power of the heart. Disease of the heart can operate in still another manner. It can impair the contractile power of the heart. Contractile power is measured by the energy liberation and the work done at a given heart size. Experience has shown that the work and the energy cost of the work are functions not only of heart size but also of the existing load. That is why these two factors should be correlated not only with heart size but with load as well. The heart with normal contractile power produces a definite amount of energy and does a fixed amount of work at a given heart size and at a given heart load. As these are increased, the energy liberation and work done increase in a definite fixed pattern. When the heart is diseased and the contractile power impaired as a consequence, the work done and energy liberated for a given load and a given heart size is decreased. The heart still increases its energy liberation and work output as the heart size and heart load are increased but at a lower level than normally.

Often the contractile power of the heart has been confused with the tone of the heart. It has been erroneously stated that the heart with a decreased contractile power has "poor tone" while one with a normal contractile power has "good tone." Tone of the heart is best defined and is generally accepted by modern physiologists as the resistance offered by the heart to filling. It can, therefore, be expressed by a curve relating the pressure existing within the fully relaxed ventricle to the volume at that time.

A decrease in contractile power with the load unchanged operates in the same manner as increasing the load of the heart with the contractile power unchanged. Compensation for such a decrease in contractile power is also the same, namely, the heart can dilate, it can accelerate and it can hypertrophy until it is enabled to meet the existing load.

The impairment of contractile power produced by disease can occur because of a decrease in the number of contractile elements, as is the case when a myocardial infarct develops or muscle units are otherwise destroyed or rendered irresponsive. It may, however, come about because of a decrease in the contractile power of the muscle units without the destruc-

tion of any fibers. The latter mechanism is by far the more common occurrence in disease.

These effects of disease on contractile power can be best exemplified in connection with figure 3. The relation of the work of the heart to the heart size is indicated in diagrammatic fashion in this figure in arbitrary units. The uppermost curve labelled I-N represents the correlation in the normal heart and in the heart of a patient rated as Class I of the American

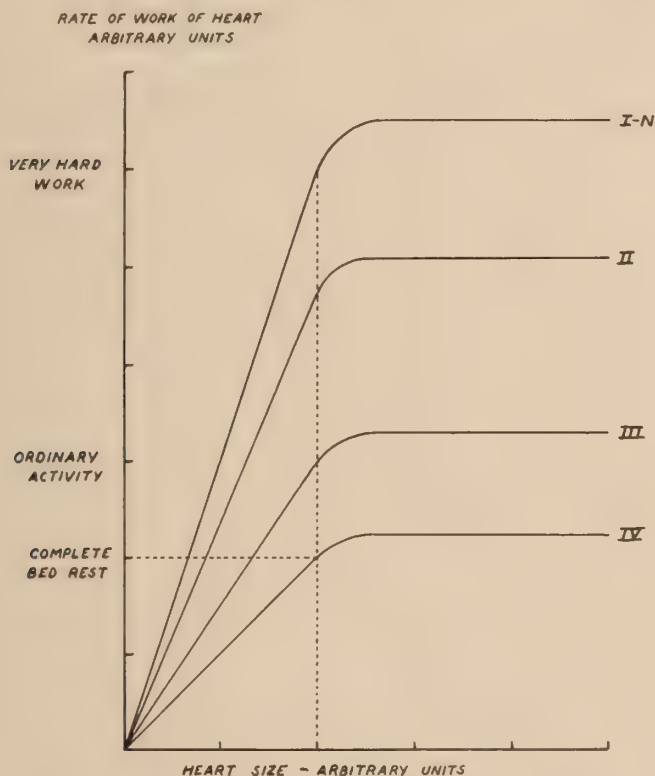


FIG. 3. Diagram showing the relation of work done to heart size in normal subjects (N) and in patients with heart disease falling into classes I, II, III and IV of the American Heart Association Classification. Discussed in text.

Heart Association Classification. In this case there is no impairment in the ability of the individual to carry on his activities. Curves II, III and IV represent respectively Classes II, III and IV of the American Heart Association Classification, that is, patients with slight restriction of activity, patients with moderate restriction of activity, and patients requiring complete bed rest, respectively. It will be seen in figure 3 that at the load on the heart during complete bed rest, the normal or Class I patient requires a smaller heart size to do the required work than the

patient in the other 3 classes. The patient in Class II requires a smaller size than one in Class III and the latter requires a smaller size than one in Class IV. Furthermore, it is apparent that the cardiac reserve in the normal or Class I subject is greater than in the Class II subject, the reserve of the Class II subject is greater than in the Class III subject and that of the Class III subject is greater than that of the Class IV subject. As is indicated in the diagram, the patient in Class IV has so limited a cardiac reserve that only a slight increase in his activity will soon exceed the maximum work capacity of his heart and lead to a vicious cycle which may ultimately end in death. Should the maximum contractile power decrease still more, the patient would be unable to meet the load existing even at complete bed rest and life would become untenable. It is possible to overburden even the normal heart and the heart in Class I so that it cannot cope with its load. The heart in Class III cannot meet the load of extraordinary activity and the heart in Class IV cannot meet the load of ordinary activity.

The chart of figure 3 also demonstrates what must happen when the load is fixed and the contractile power decreases. If we follow the horizontal dotted line at the level called complete bed rest, it will be seen that as the patient changes from Class I to Class IV, with its associated decrease in cardiac contractile power, the only way in which the load can be met and the work of the heart maintained at this level, is by an increase in heart size. Similar charts could be constructed with relation to heart rate and cardiac hypertrophy and the analysis would be on identical lines.

We are now in a position to discuss the possible changes that can occur when the contractile power of the heart is impaired. First, the heart does less work, and this is mirrored in a fall in arterial blood pressure or in cardiac output, or both. This happens clinically and we have seen it in our animal experiments. If the decrease in contractile power affects the right heart, these manifestations will first appear on the right side, but quickly equilibrium is established and the manifestations then appear on the left side also. The same is true if the left heart is the one with a decreased contractile power, the manifestations, however, first appear on the left side.

Often, however, instead of a decrease in work, the work is maintained when the contractile power of the heart is depressed, hence the arterial pressure does not fall and the cardiac output does not decrease. Instead congestion appears in that part of the circuit behind the pump whose contractile power is impaired. Thus, congestion will appear in the lungs when the contractile power of the left heart is impaired and in the systemic veins when the contractile power of the right heart is reduced, or in both when both pumps are impaired.

The congestion is in fact the immediate compensatory mechanism by which the heart size is increased sufficiently to maintain the cardiac output. In this way the work level of the heart can be kept unaltered and the sole

evidence of the impairment of contractile power that will remain is congestion. This is the usual state of affairs observed clinically.

This congestion and the increase in heart size may be the sole evidence of impaired contractile power. Often, however, tachycardia and cardiac hypertrophy may also appear. The latter two, in fact, will tend to lessen the degree of congestion and the size of the heart if their limits are not too closely encroached upon. In acute heart failure and in myocardial infarction in which the manifestations of impaired contractile power appear in the form of a decreased work without congestion, tachycardia will also tend to serve as a compensatory mechanism to increase the work output of the heart.

The important concept, that cannot be stressed too much, is that an impairment in the contractile power of the heart may appear; 1) without congestion in any part of the circuit but only with a decrease in the work level of the heart, or, contrariwise, 2) with *only* congestion in the systemic, pulmonary or both venous circuits with no decline in the work level of the heart. Of course, it is true that both a decrease in work level and congestion may occur simultaneously.

Heart failure, its manifestations and its fundamental cause. Heart failure is a manifestation of impairment of contractile power. It is evidenced by a change in the ratio of work done by the heart to the heart size (or to the venous pressures).

In the clinical evaluation of heart failure, attention should, therefore, be paid to both the work done by the heart and the degree of venous engorgement as well as the heart size. Venous engorgement in the systemic circuit is manifest by liver enlargement and visibly enlarged neck veins, and when chronic it leads to edema in the dependent parts of the body and to ascites. In the pulmonary circuit venous engorgement causes a decrease in vital capacity, a decrease in breath-holding time, and it may lead to râles in the chest. Of course, other circumstances than heart failure may be responsible for these manifestations and the differentiation becomes the problem of the clinician. To use but one illustration, mitral stenosis without heart failure is accompanied by pulmonary congestion. Failure to recognize this has been responsible, as much as anything else, for confusion in differentiating right from left heart failure.

The work of the heart can be roughly estimated clinically by the product of cardiac output and the pressure in the systemic and pulmonary arteries. The cardiac output is indicated by the circulation time, ballistocardiograph, or by actual direct measurement. The systemic arterial pressure can be measured directly. The only measure of the pulmonary arterial pressure clinically available is the intensity of the second pulmonic heart sound. In evaluating the cardiac work cognizance must also be taken of the hidden work, such as that done in overcoming obstructions or that lost in regurgitation.

When a crude clinical estimate is made of venous engorgement in relation

to the work done by the heart, a rough measure of the presence and magnitude of heart failure is obtained. It is not obtained by consideration of each alone. A similar assay can be made of heart failure by correlating the work done by the heart with its size. Obviously in the estimate of heart size the size of the ventricles is by far the most important criterion, and x-ray examination and fluoroscopy are extremely valuable for this.

From these considerations it is apparent that since heart failure may manifest itself by a decrease in cardiac work without venous engorgement or by an unchanged cardiac work with venous engorgement, heart failure is determined neither by congestion alone nor by decreased work alone but by the ratio between the two. For example, the normal heart may have venous engorgement but this is associated with an increased cardiac work. The normal heart may also do a decreased amount of work but this is associated with a decrease in venous return. Therefore, knowledge only of the amount of cardiac work or of the venous engorgement (or size of the heart) is not sufficient in the assay of the presence or degree of heart failure. This assay requires that the two be correlated, at least roughly and this is not done sufficiently clinically.

In considering the fundamental mechanism responsible for heart failure resulting from impairment in contractile power of the heart, two possibilities exist; 1) that the heart releases the normal quantity of energy for the size of the heart or the existing load, but that the efficiency with which this energy is converted into work is reduced, or 2) that the primary mechanism is a decrease in the energy release for the size of the heart or its load, without the mechanical efficiency being altered.

In the past few years, we have been concerned with an assay of the fundamental mechanism involved in heart failure. Our results clearly point to the fact that failure of the heart appears to be primarily an impairment in the release of energy (as measured by oxygen consumption) and not a reduction in the mechanical efficiency of its conversion to work. We have, therefore, concluded that impairment of contractility, which is the basis of heart failure, means impairment of energy release and that changes in mechanical efficiency are secondary to the circumstances altering the relative input-load and resistance-load.

It has been pointed out earlier that the mechanical efficiency of the heart tends to improve when the input-load is increased but tends to decline when the resistance-load is augmented. When the contractile power of the heart is decreased, and heart failure develops, the relative load on the heart is increased. The mechanical efficiency will increase, decrease or remain unchanged, depending on whether the relative increase in load involves the input- or the resistance-load to the greater extent. This may explain some of the discrepancies appearing in the literature regarding changes in mechanical efficiency accompanying heart failure. Since most

instances of heart failure have no decrease in input-load, the mechanical efficiency usually does not decrease.

Regardless of how the mechanical efficiency of the heart changes, the primary mechanism responsible for heart failure appears to be the impairment in energy release of the heart and not an impairment in its conversion to work.

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SPONTANEOUS PERIRENAL HEMATOMA

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An uncommon feature of kidney disease is spontaneous hemorrhage into the perirenal tissues. When this occurs it may cause considerable difficulty in diagnosis, so that it is well to be familiar with the clinical features of the condition in order that it may be recognized and treated promptly. At this time, I report my observations in 3 cases and review some of the important literature on the subject. Before presenting the cases it will be appropriate to say something about the etiology of spontaneous perirenal hematoma.

ETIOLOGY OF SPONTANEOUS PERIRENAL HEMATOMA

In 1933, Polkey and Vynalek (1) collected the cases of spontaneous perirenal hematoma which had been reported in the literature up to that time. Those listed as due to kidney disease included nephritis, tumors, tuberculosis, nephrolithiasis, and cystic disease. Among those resulting from extrarenal disease, aneurysm of the renal artery, arteriosclerosis of the aorta, and pancreatitis were the common causes. Hematomas in this region were also found in patients with saccular aneurysms of the aorta, hemophilia, leukemia, or other hemorrhagic diseases. In view of this report, it may be assumed that the commonest cause of spontaneous perirenal hemorrhage is some type of kidney disease. The most frequent extrarenal causes are arteriosclerosis and aneurysm of the renal artery. In the following 3 cases, the primary lesion was in the kidney.

CASE REPORTS

Case 1. A 35 year old man with hypertension developed pain and a mass in the left flank, fever, and anemia. Operation disclosed a massive hematoma about the kidney. Nephrectomy. Complete recovery.

History. The patient was admitted to the Evans Memorial Hospital in March, 1940, complaining of stiff and painful joints. Three weeks before admission he had a sore throat, which was followed within a few days by pain in the joints of the hands and feet. He had also noted increasing weakness, malaise, fever, sweats, and recurrent attacks of pain in the left flank.

The past history disclosed recurrent osteomyelitis of the left tibia since childhood, the last attack being at the age of 27 years (8 years before the present illness). At the age of 25 it was discovered that the patient had hypertension. During the past few years he had noted frequent epistaxis and recurrent headaches, and for at least 8 months he had had recurrent attacks of pain in the left flank.

Examination. The patient was a pale man who appeared to be acutely ill. The temperature was 98.4 F., the pulse 120, respirations 30, and the blood pressure 200 systolic and 134 diastolic. The skin was warm and moist. The ocular fundi showed tortuous vessels with narrowing of the lumen, several flame-shaped hemorrhages in the left fundus, and scattered exudate. There was a moderate degree of oral sepsis and the tonsils were enlarged. The chest was symmetrical, but the left diaphragm was elevated and there were a few râles on deep inspiration over the left lower lobe. The heart was enlarged to the left, measuring 10.5 cm. from the midsternal line. The rhythm was regular and the sounds were distinct and clear except for a Grade 1 systolic murmur at the apex. The abdomen was not distended, but in the left upper

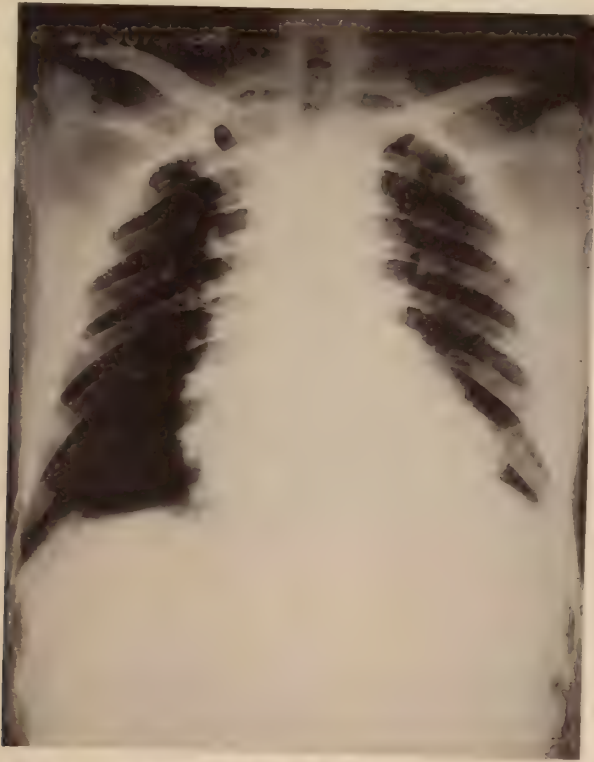


FIG. 1. Chest plate showing dilated aorta and elevation of the left dome of the diaphragm

quadrant there was a firm, rounded mass which extended well into the flank. There was tenderness over it but it did not move with respiration. The spleen was not felt and there was no abdominal distension. The rectal examination showed nothing abnormal, and aside from the well-healed scars over the anterior surface of the left tibia, the site of previous operations for osteomyelitis, the extremities were normal.

Laboratory Data. The urine was acid, normal in color, contained large amounts of albumin, a few casts and leucocytes. There were no red blood cells. On admission the red blood cell count was 3,140,000, the hemoglobin 45 per cent, and the white blood cell count 19,000, with 89 per cent polymorphonuclear cells. The blood Hinton reaction was negative. X-ray examination of the chest showed an elevation of the left side of the diaphragm and moderate enlargement of the heart (fig. 1). Intra-

venous pyelograms showed the right kidney shadow to be slightly enlarged and there was dilatation of the pelvis and calyces, with some blunting. The left kidney shadow



FIG. 2. Pyelogram showing a poorly functioning left kidney and shadow about the left kidney obscuring its outline

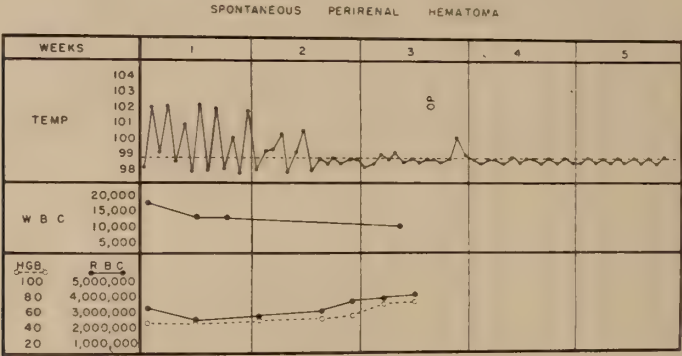


FIG. 3. Chart of temperature, leucocyte and red blood cell count, and hemoglobin content (Case 1). OP—Operation.

was considerably enlarged; the pelvis and calyces were poorly defined (fig. 2). The left tibia showed a healed osteomyelitis.

Course. The course of the temperature, the red and white cell counts, and the hemoglobin is shown in figure 3. During the first 10 days of observation the tem-

perature fluctuated between 98.4 and 102°F. There was a gradual decrease in the leucocyte count and the blood returned to normal after four blood transfusions. During the third week Dr. Samuel Vose explored the left kidney region and found a large perirenal hematoma. The left kidney together with the organized blood clot was removed. Following the operation the patient made an uneventful recovery.

Pathology. The examination of the surgical specimen was made by Dr. Charles F. Branch, who reported as follows: "The specimen consisted of a kidney surrounded by a large blood clot. The kidney measured 10.0 x 4.5 x 3.5 cm. and weighed 150 gm. It was firm, smooth, and pale reddish-brown, and on section showed a normal relation between the pyramids and the cortex. The entire kidney was surrounded by a large amount of old and recently clotted blood with clots apparently largest about the lower pole. Careful dissection of the kidney failed to reveal an abscess, neoplasm, or any rupture. The blood had more or less completely dissected the capsule from the kidney and had also ruptured through into the surrounding perirenal tissues, so that the perirenal blood clot measured about 8 cm. in thickness. The kidney capsule was thick, fibrous, and showed definite evidence of organization of blood clots. The renal artery was intact and showed no evidence of gross arteriosclerosis. The pelvis and ureters were negative."

Microscopic Examination. Sections through the kidney cortex showed very little change other than that associated with compression and hemorrhage. A few glomeruli were cirrhotic; the tubules were atrophic or absent, with a relative increase in connective tissue and an infiltration with small numbers of leucocytes in certain areas. In general, however, the glomeruli and tubules were well preserved. The epithelium was intact; the lumina contained a moderate amount of amorphous debris and rare hyaline, pigment, and red blood cell casts. The collecting tubules presented occasional areas of pigmented epithelium and rare minute foci of calcification. The blood vessels showed a well-marked fibrosis and hyaline thickening of the intima, in places so extensive that it almost occluded the lumen. The capsule was separated from the kidney surface, and there was a massive blood clot between it and the cortex. The precise origin of the hemorrhage was not determined, although in the lower pole there was a slight depression which had the appearance of a small cavity. It was lined with thick fibroelastic tissue which suggested a cross-section of the wall of a blood vessel. At one point in this area the lumen of the vessel was occluded by a partially organized thrombus. The inner portion of the wall showed a dense fibrous thickening. It was concluded that the hemorrhage arose from the lower pole of the kidney, probably as the result of a rupture of a blood vessel.

Comment. In brief, a man thirty-five years of age who had been known to have had osteomyelitis and hypertension in the past came under observation for fever, malaise, weakness, and recurrent pain in the left flank of several weeks' duration. On examination it was found that he had an anemia, irregular fever, and a mass in the left flank which did not move on respiration and which on pyelography seemed to be an enlarged left kidney. With the above history and the other findings, two diseases were suspected: a perinephric abscess and a tumor of the kidney. In view of the previous history of staphylococcal osteomyelitis of the left tibia followed by fever, anemia, and a mass in the left flank with recurrent attacks of pain in this region, a perinephric abscess secondary to a carbuncle of the kidney seemed likely. The hypertension and a mass in the left flank with fever and leucocytosis likewise suggested a renal tumor. A definite preoperative diagnosis of perirenal hematoma was not made.

It would appear, then, that this patient had hypertension with moderate vascular disease involving the kidney and that the vessels near the surface of the kidney had ruptured spontaneously, producing a large blood clot between the cortex and the capsule, finally rupturing through the latter into the perirenal tissues.

Case 2. A 56 year old man with right-sided hydronephrosis, nephrolithiasis, and pyelonephritis had a sudden attack of pain in the flank, followed by the development of a mass in the abdomen, anemia, and hematuria. Death followed operation.

History. The patient was admitted to the hospital complaining of pain in the right flank. He had been well until two years before admission, when he began having attacks of right-sided renal colic with hematuria. Examination at that time revealed a stricture of the right ureter with a hydronephrosis, and an attempt was made to relieve him by dilatation of the stricture. Nine months later he was found to have a calculus in the right kidney pelvis, which was removed. He remained in reasonably good health except for recurrent attacks of pyelonephritis on the right side.

Ten days before admission the patient was riding in a train when he was seized with a severe attack of pain in the right side of the abdomen and flank. It was severe and continuous, and radiated through the abdomen and up the back. The pain was soon followed by dysuria, frequency, and hematuria. Chills and fever, with repeated attacks of vomiting, were present for four days.

Examination. The patient appeared to be acutely ill. The skin was pale with an icteric tinge. The temperature was normal, the pulse rate was 72, and the respirations were 28. The heart and lungs were normal. The abdomen was full and asymmetrical, the right side being larger than the left. There was a large mass in the right flank extending from below the liver to within 4 cm. of the umbilicus and down to the crest of the ileum. It was fixed, and pressure over it caused pain and discomfort.

Laboratory Data. The red blood cell count was 2,500,000 and the hemoglobin 45 per cent. The leucocyte count was 56,400. The urine contained pus and many erythrocytes, and the blood urea nitrogen was 100 mg. per 100 cc.

Course. Operation was performed and a large perirenal hematoma was found. Following the removal of the blood clot and blood transfusion the patient continued to vomit, and died within six hours after operation.

Necropsy Findings. The necropsy showed stenosis of the left ureter with hydronephrosis of the left kidney pelvis; obstruction of the right ureter with hydronephrosis, pyelonephritis, nephrolithiasis, and pyoureter; cystitis; perirenal hemorrhage; and jaundice.

Comment. In brief, a man of fifty-six years, who was known to have kidney disease had a sudden severe pain in the flank and abdomen, soon followed by collapse, fever, chills, and hematuria. Within a few days a large mass developed in the abdomen and there was anemia, leucocytosis, and jaundice. Operation disclosed a massive perirenal hematoma, and necropsy showed that the hemorrhage arose from the surface of the right infected kidney.

This is an example, then, of a spontaneous perirenal hematoma resulting

from the erosion of a vessel in the kidney. There was not only bleeding into the perirenal tissues but hematuria as well.

Case 3. A 53 year old man with *periarteritis nodosa* developed severe pains in the left upper quadrant of the abdomen and the lower part of the left chest. He failed rapidly. Necropsy showed a massive perirenal hematoma.

History. The patient was first seen five months before death complaining of cough, expectoration, and distress in the thorax. For at least five years he had had recurrent attacks of cough, dyspnea, expectoration of mucoid sputum, and increasing malaise and exhaustion. Within recent months he had had two attacks of paroxysmal nocturnal dyspnea. For one week he had had frontal headache, nasal obstruction, and pain over the right eye.

The past history was essentially negative, except for the fact that the patient had been a brass-molder for 26 years and had been exposed to silicate dust and fumes from molten brass, from which he had "brass chills" occasionally.

Examination. The temperature was 99.4°F., pulse 80, respirations 20, and blood pressure 130 systolic and 85 diastolic. The patient was a well nourished and well developed man, propped up in bed, coughing occasionally, and the respirations were labored with rhonchi. When he coughed he raised a moderate amount of mucoid sputum. There was slight pain on pressure over the maxillary sinuses. The right conjunctiva was injected. The teeth were carious and there was moderate pyorrhea. Bilateral nasal obstruction due to hypertrophy of the mucosa over the turbinate was present. The throat was clear. The chest was enlarged. The respirations were thoracic in type and there was some hyper-resonance over both bases and many fine bronchial râles throughout both lungs. One could hear both inspiratory and expiratory rhonchi and sibilant râles with prolonged expiration. The heart sounds were distant, but otherwise examination of the heart was negative. The abdomen showed nothing abnormal and the extremities, genitalia, and reflexes were normal.

Laboratory Data. The urine had a specific gravity varying between 1.010 and 1.020. The red blood cell count was 4,600,000 and the hemoglobin 85 per cent. On smear, the red blood cells and platelets appeared normal. The white blood cell count varied from 12,000 to 13,000; polymorphonuclear leucocytes, 54 per cent; lymphocytes, 17 per cent; mononuclears, 13 per cent; eosinophiles, 14 per cent; and basophiles, 2 per cent. The eosinophile count varied from 13 to 16 per cent. The Kahn reaction was negative. The non-protein urea nitrogen was 32 mg. per 100 cc. There were no tubercle bacilli in the sputum. The vital capacity varied between 1.60 and 1.85. A tuberculin test, 1:20,000, was positive. X-ray examination of the sinuses showed both antra to be cloudy. The chest showed marked peribronchial markings extending out from both hila. A tentative diagnosis of pneumoconiosis was made. Later another x-ray examination of the chest showed an enlarged shadow at the hilum, with mottling about the root of the lung. Old tuberculosis of the right-upper lung field was also observed. Lipiodol injection showed no evidence of bronchiectasis.

Course. Attempts were made to relieve the nasal obstruction by drainage of the sinuses and submucous resection of the turbinate. The patient was discharged after two weeks' observation, but returned four months later complaining of progressive weakness and failure to regain his strength. About four months before death he complained of a tingling sensation in the feet, and this gradually spread up both legs. Soon afterward the fingers became involved and the patient had difficulty in buttoning his clothes. The tingling sensation was more or less constant and so severe that he had difficulty in getting out of bed. He later developed wrist drop,

particularly on the left. His cough persisted and he noted that he was becoming pale and progressively weaker.

Physical examination now showed that the temperature was normal, the pulse 100, respirations 22, and blood pressure 180 systolic and 110 diastolic. The patient had lost a considerable amount of weight and appeared acutely ill. The lungs continued to show râles, as they had on previous examination. Neurological examination showed clumsiness of the fingers, astereosthenosis, and diminution of vibratory sense over the feet and legs. A small number of nodules were felt along the inner aspect of the arm. There were also a few subcutaneous nodules on the forehead and on the back along the spinal column.

Laboratory examinations were essentially the same as on the first admission, except that the eosinophiles were only 4.5 per cent and anemia had developed, with a red blood cell count of 3,600,000, a white blood cell count of 17,650, and the hemoglobin 42 per cent. X-ray films of the chest showed increased fibrosis of both lower lung fields. The long bones of the skull were negative.

During the first few days of observation, the temperature varied between subnormal and 100.4°F., the pulse between 80 and 110, and respirations between 20 and 28 per minute. The patient was extremely weak and continued to complain of numbness and tingling of the extremities. Five days after admission he developed a wrist drop on the right side. On the ninth day it was found that there were firm, tender nodules along the brachial artery of the right arm. On the morning of the day of death the patient complained of a sudden severe pain in the upper part of the abdomen on the left side, extending into the left flank and the left lower part of the chest. This was soon followed by weakness and increasing respirations. The temperature was subnormal, the pulse rate 92, and within three hours he died without developing any signs of a mass in the left upper quadrant.

Necropsy Findings. There was an extensive perirenal hemorrhage arising from the left kidney; periarteritis nodosa involving the vessels of the kidney, liver, mesentery, and mitral valve; perirenal hematoma on the left; slight serosanguinous ascites; bronchopneumonia; pulmonary congestion and edema; emphysema; anthracosis; anemia; slight hypertrophy of the femoral marrow; and slight generalized enlargement of the lymph nodes.

Comment. A man fifty-three years of age, had had recurrent attacks of chronic cough, expectoration, and asthma with eosinophilia, developed hypertension, signs of peripheral neuritis, progressive loss of weight, and small nodules along the brachial artery, over the forehead, and over the spine. He had an anemia with leucocytosis and attacks of asthma with eosinophilia. On the day of death he was seized with a severe pain in the upper part of the abdomen on the left side and died within three hours. The necropsy showed the characteristic lesions of periarteritis nodosa involving, among other structures, the kidney and a massive perirenal hematoma.

Perirenal hemorrhage as a fatal complication of periarteritis nodosa has been described by Weaver and Perry, (2) who stated that they were able to find descriptions of 8 cases of periarteritis nodosa in which death was due to renal or perirenal hemorrhage. It is well to remember, then, that any patient with periarteritis nodosa who complains of sudden pain in the flank followed by progressive weakness may have hemorrhage into the perirenal tissues resulting from a rupture of one of the vessels of the kidney or the surrounding structures.

DISCUSSION

For purposes of discussion, perirenal hematomas are usually divided into two groups: traumatic, and non-traumatic or spontaneous. The cases following trauma have been discussed thoroughly by Sohn (3), Joyce (4), Bailey (5), and Cole (6), and an excellent review of the subject of the spontaneous perirenal hematomas has been made by Polkey and Vynalek (1).

Cases of post-traumatic perirenal hemorrhage are becoming more frequent and important on account of the increasing number of automobile accidents. Every surgeon who has studied these cases stresses the difficulty of distinguishing between peritonitis and the retroperitoneal process. One of the reasons for the confusion is due to the association of paralytic ileus with retroperitoneal hemorrhage. A small number of such patients have been operated on for a suspected intra-abdominal lesion and only an inhibition ileus has been found (3, 4 and 6).

It has been shown by Demel (7) that the presence of blood in the retroperitoneal space, especially in the region of the splanchnic nerves, will cause meteorism of the intestines, and Cole (6) has reported cases in which it was impossible to exclude peritonitis before abdominal operation. Abdominal pain and muscle spasm were present in all cases. It is impossible, therefore, in the cases that occur after injury to decide from the symptoms and signs alone whether or not an early peritonitis is present. Among other reasons for the difficulty in diagnosis in the post-traumatic cases is the fact that there may be no anemia and that a mass may not have developed. If hematuria is present, the possibility might be considered. When in doubt, the diagnosis is made by means of surgical exploration.

In the non-traumatic or spontaneous forms of the disease, the onset may be sudden or insidious. In two of the cases reported the onset was sudden, but in the third it was insidious. When the onset is sudden, there is an acute attack of pain in the region of the kidney, often associated with nausea and vomiting, the symptoms and signs of internal bleeding, and the development of a mass in the flank. Fever and leucocytosis are common within a few days after the onset of the bleeding, and this may continue for some days, as in Case 1. Rigidity of the muscles about the costo-vertebral angle and the upper part of the abdomen is often present, especially in cases associated with renal disease or infection. Lumbar swelling and ecchymosis are infrequent, but such signs are distinctive when they occur.

In some of the cases described in the literature, abdominal distension, vomiting, and disturbance of the bowel habits are observed. Jaundice may be present, as in Case 2. Hematuria is infrequent unless there are lesions in the pelvis or other parts of the kidney to account for it. The findings in the urine depend upon the pre-existing renal disease.

In most of the reported cases, the course of the disease is that of a rapidly progressive hemorrhage, as in Cases 2 and 3, but in some it is more chronic,

as in Case 1. In the vast majority of cases the patients die within a few days unless the kidney is removed and the hemorrhage is controlled. In a few, the process becomes chronic and organization of the blood clot with or without calcification follows (8). These cases are usually the post-traumatic ones. The late features of the process are of interest and will now be discussed.

LATE FEATURES OF PERIRENAL HEMATOMA

It has been stated above that most patients who develop perirenal hematoma die unless they are operated on and the bleeding is controlled. Naturally spontaneous hemorrhage is much more serious on account of the underlying lesion which is responsible for it. That some patients recover after the development of a large perirenal hematoma, without operation, is clear from the report of Colston (8), which deals with calcified cysts of the kidney. He discusses calcified cysts in the retroperitoneum which were about the kidney. In each case there was an antecedent history of a severe injury varying from two and one-half to thirty years. A mass was palpable in the flank in four cases and the calcium deposits were found by x-ray examination.

Colston traces the sequence of events in these cases somewhat as follows: After an injury to the kidney there is a hemorrhage which ruptures through the capsule of the kidney into the surrounding tissues. The hematoma may then either be absorbed or undergo organization and calcification. The calcium is deposited about the periphery of the hematoma as well as in the central portion. The wall consists of fibrous tissue with irregular areas of calcification and fibrous tissue without an epithelial lining. To the pathologist, the latter feature is important in differentiating the calcified mass due to an organized blood clot and a simple cyst with a hemorrhage into it. True cysts are lined with epithelium.

The natural history of a hematoma about the kidney, then, may be complete absorption, organization, and calcification (pseudo-cyst formation) or death from continued bleeding or the underlying disease. The proper treatment when the condition is recognized is surgery.

In short, the diagnosis of a perirenal hematoma may be made if a patient with or without known kidney disease suddenly has an attack of *pain in the region of the kidney which is followed by the signs of internal hemorrhage and a mass in the flank*. In the cases following trauma, the history of an injury followed by abdominal pain and distension with vomiting and the signs suggesting an internal hemorrhage, together with pain in the flank, are all suggestive. In these cases the location of the hemorrhage is made by operation. If recovery follows without operation, the hematoma may organize and finally calcify.

SUMMARY AND CONCLUSIONS

Spontaneous perirenal hematoma may occur during the course of disease of the kidney.

Three cases are described. One occurred as a complication of nephrolithiasis and pyelonephritis, one as a complication of periarteritis nodosa, and a third during the course of hypertension with vascular disease.

The diagnosis is based on three points: The sudden onset of pain in the region of the kidney, the symptoms and signs of internal bleeding, and the appearance of a mass in the region of the kidney.

The treatment is surgical, and the prognosis depends upon the underlying disease of the kidney and the degree of hemorrhage.

Hemorrhage about the kidney in the retroperitoneal space may also arise from the aorta, the suprarenal glands, or the pancreas.

Hematomas about the kidney may be completely absorbed or they may undergo organization and calcification. The diagnosis in these cases is made from the previous history of an injury, the presence of a mass in the flank, and a calcified area in the region of the kidney that is detected by x-ray examination.

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THE SIGNIFICANCE OF PLASMA AND BLOOD VOLUME STUDIES IN CLINICAL MEDICINE

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In the autumn of 1914 several of us who were members of the staff of Johns Hopkins Hospital were interested by our chief, Dr. Janeway, in studying the problem of total blood volume in essential hypertension. At that time certain investigators had even postulated that the cause of the increased blood pressure was an abnormally large blood volume.

Leonard Rowntree suggested the use of the phthalein compound, tetrachlorophthalein, as a possibility for developing an indirect method for the estimation of blood volume. I remember well our first experiment. About ten minutes after an initial intravenous injection of this phthalein into a dog, a sample of plasma revealed considerable color but within half an hour only a faint trace of color was present. This led to our consulting Dr. Herbert Evans, the anatomist, who at that time was keenly interested in vital staining dyes. He informed us that he was then experimenting with a dye, vital red, which he had observed persisting in the blood of a rat for many days and that such a rat seemed perfectly healthy. He kindly gave us some of his stock of vital red, and we soon learned that in the normal individual the dye disappeared slowly from the blood stream and had little or no toxicity.

Rowntree and I realized that although we had in our possession a dye that might prove useful in estimating total blood volume, there were many facts connected with its use that required study. These included mixing time, disappearance from the blood stream and mode of excretion. We were surprised to find that the dilution of the dye in the plasma of the dog and in normal human subjects gave very low values for total blood volume when compared with those obtained by former direct washing out methods. This fact suggested that dilution of the dye might be limited to the plasma and that the dye did not enter the red blood cells. Further experiments proved this supposition to be correct and in order to estimate the total blood volume, the hematocrit was employed to determine the relation between the volume of plasma and erythrocytes. So much for the inauguration of a dye method for estimating plasma and total blood volume (26).

Meek and Gasser in 1917, while working on the problem of experimental shock, realized the importance of estimating blood volume in this condition and devised a method using solution of acacia. They were able

to show that the rate of disappearance of the injected acacia was slow and, together with Erlanger, that its concentration was increased abnormally in shock (7). This latter finding indicated a reduced blood volume.

Since 1914 much has been accomplished in perfecting the dye method. Several groups of investigators have added greatly to its accuracy and made the actual estimation easier and more satisfactory. These investigators include Harris, Smith and Whipple (4, 21) and their co-workers, Rowntree, Brown and Roth, Gregersen and his co-workers (14-17), Gibson and Evans, Sunderman and Austin, and in the last year Robinow and Hamilton, and the biochemist Harington and his co-workers. However, all of these workers are also quite ready to admit that the perfect dye and its method of estimation in the blood have not yet been found (6, 14).

In 1935 Power (25) of our laboratory devised a simple reliable quantitative method for determining the concentration of acacia in small amounts of serum. After the method had been devised, he and I waited for a favorable opportunity to inject acacia into normal subjects and estimate its disappearance curve from plasma. Two years ago such an attempt was made. It was soon evident that solutions of acacia, even in the small doses we injected, caused in these subjects an allergic reaction in the form of urticaria. Small repeated doses of histamine were then given to a group of four normal persons and subsequently solution of acacia was injected. Urticaria did not occur. A satisfactory disappearance curve was obtained in one subject. Like that of Meek and Gasser in the dog (fig. 1) the curve showed a slow drop during the first hour (fig. 2). The concentration in the twenty minute sample was chosen for plasma volume estimation. In this subject and three others the plasma volume ranged from 33 to 52 cc. per kilogram of body weight. These plasma volumes and disappearance curves were not unlike those obtained with the dye method (10, 26, 30) (fig. 3). Some changes in the constituents of the blood after the simple intravenous injection of 40 cc. of solution of acacia are shown in table 1. Further estimations are planned. Dr. Power and I, therefore, believe that acacia can be used in this manner for the estimation of the plasma volume of nonallergic persons. It may have certain advantages over the dye method (24).

Before dismissing the question of methods of estimating blood volume, I should like to suggest that a dye or acacia-like substance containing a chemical radical easily determined quantitatively, such as iodine, might offer the ideal substance for the indirect estimation of blood volume.

The determination of plasma and blood volume by the dye method has given us a much clearer insight into certain mechanisms which occur in anemia. After a simple hemorrhage the blood volume may be restored almost immediately and it is only in the subsequent twenty-four hours that the number of erythrocytes diminishes (table 2). If the hemorrhage is large and is accompanied by trauma, the usual rapid inflow of fluid may

be delayed, and plasma and blood volume may be reduced for a time but later restored. In such a person the plasma volume may be even greater for a few days than normal, seeming to compensate partially for the reduced red cell volume (22). Bennett and his associates, on the other hand, found

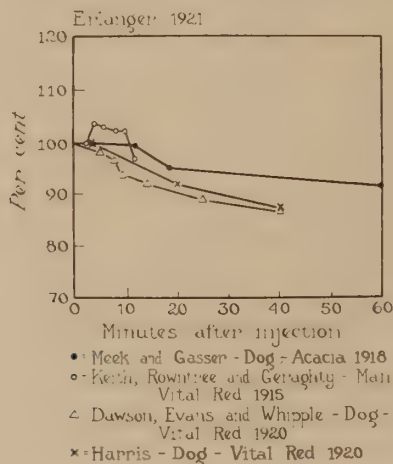


FIG. 1. Four disappearance curves following intravenous injection of solution of acacia or the dye vital red. (Redrawn from Erlanger, *Physiol. Rev.*, 1: 177-207, 1921.)

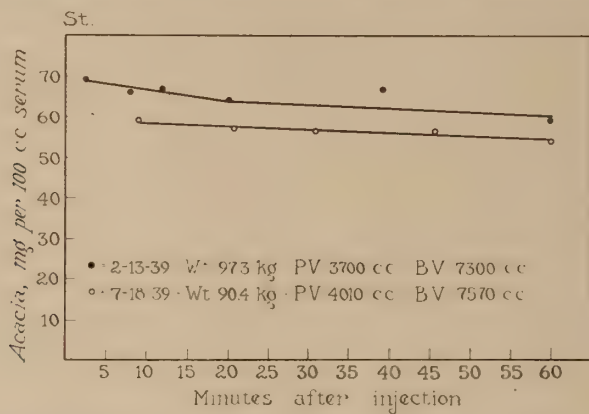


FIG. 2. Two disappearance curves of acacia in the same normal subject. Estimations for curves made approximately five months apart. (Keith and Power, unpublished data, 1939.)

that after severe gastric hemorrhage the plasma volume never rose above the normal level. As recovery from hemorrhage continues, the plasma volume gradually decreases; the erythrocyte volume rises and at the end of approximately three weeks all three, the plasma, erythrocyte and total blood volumes, reveal normal values (fig. 4). An interesting observation on soldiers suffering from wound shock and hemorrhage was that among

those patients receiving large infusions of solution of acacia the plasma volume rose immediately to higher levels and the increased volume of plasma persisted longer than among those who did not receive solution of acacia (22) (fig. 5). This observation is in agreement with the fact that acacia is removed relatively slowly from the circulation and while present

TABLE 1

Changes in certain constituents of the blood after intravenous injection of 40 cc. of 6 per cent solution of acacia

SUBJECT	TIME	HEMATOCRIT READING, PERCENT OF ERYTHROCYTES	BLOOD SERUM		
			Acacia	Total nitrogen	Chlorides
	minutes		mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.
B	0	45.7		1,091	378
	10	44.1	68.8	1,052	378
	20	44.0	67.0	1,046	385
	31	43.9	67.0	1,031	380
St.	0	47.9		1,264	365
	9	45.8	59.1	1,186	370
	21	45.2	57.0	1,107	367
	31	46.3	56.5	1,072	370
	60	45.5	54.1	1,105	370

(0 = before injection or control.)

TABLE 2

Some effects of simple hemorrhage: phlebotomy in arm; man, aged 19 years

DATE, 1918	TIME	BLOOD PRESSURE, MM. MERCURY		PULSE RATE	HEMATOCRIT READING, PER CENT OF ERYTHROCYTES	PLASMA VOLUME	BLOOD VOLUME
		Sys- tolic	Dias- tolic				
						cc.	cc.
8 4	Before phlebotomy	120	80	60	37	3,710	5,890
	880 cc. removed from vein						
	1 hour after phlebotomy	120	80	60	37	3,820	6,060
8 5	24 hours after phlebotomy	100	65	64	35	3,420	5,260
8/11	7 days after phlebotomy	120	75	68	32	3,660	5,380

in sufficient concentration tends to increase the actual volume of plasma (25).

In chronic anemias, which include pernicious anemia and secondary types, the process of recovery as indicated by a rise in the erythrocyte volume is accompanied initially often by a large plasma volume. As the erythrocyte volume continues to rise, the plasma volume decreases and we have a similar process to that occurring after a simple hemorrhage (figs. 6, 7, 8 and 9). These volume changes among patients that have

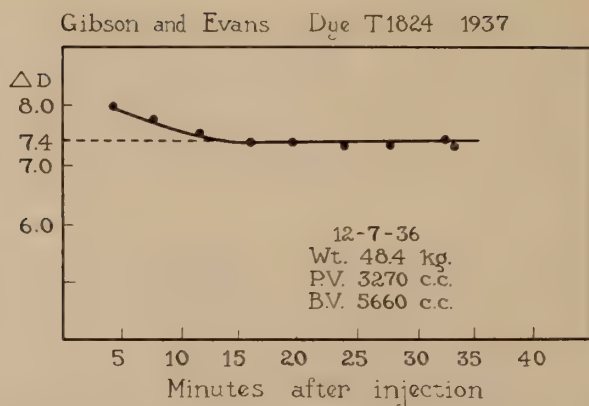


FIG. 3. Disappearance curve of Dye T-1824 in normal subject. (Redrawn from Gibson and Evans, *J. Clin. Investigation*, 16: 317-328, 1937.)

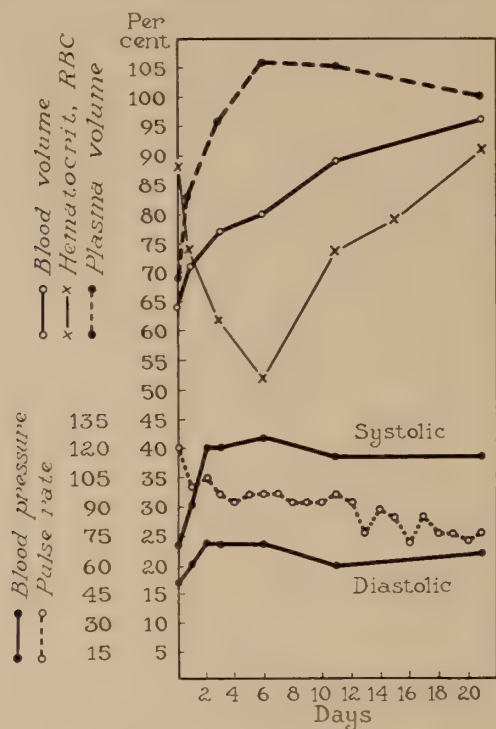


FIG. 4. A case of severe primary hemorrhage with associated wound shock. Changes in plasma volume, blood volume (dye method) and hematocrit during recovery. Note early increase of plasma volume. (Redrawn from Keith, Medical Research Committee, Special Report Series Number 27, 1919.)

anemia thus afford a definite basis for proper treatment. If the patient is in shock, the primary need is for fluid to increase the circulating plasma, while after that portion is restored, the cellular elements of the blood are then most needed.

Our original objective twenty-five years ago was to study blood volume in relation to a clinical condition or disease, essential hypertension. Therefore in the early work after establishing normal control values, we did make several plasma and blood volume determinations on hypertensive

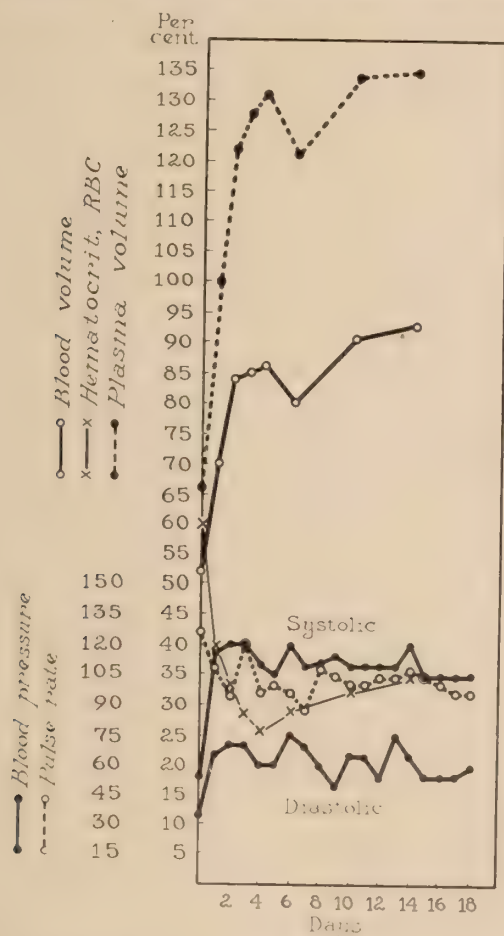


FIG. 5. A case of severe primary hemorrhage with associated severe wound shock. Changes in plasma volume, blood volume and hematocrit during recovery. Solution of acacia was injected intravenously after the initial estimations. Note prolonged increase of plasma volume. (Redrawn from Keith, Medical Research Committee, Special Report Series Number 27, 1919.)

persons. Our results and those of others since have revealed values within the normal range (19, 26, 30). A few cases of anemia and other clinical states were also studied, but the supply of vital red soon ran out and no more could be procured then.

Since then the blood volume has received due consideration in the study of many different clinical states (table 3). It is diminished definitely, as

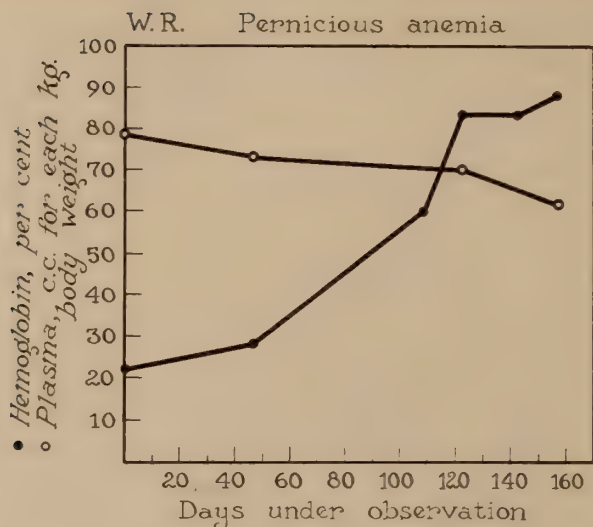


FIG. 6. A case of pernicious anemia. Changes in plasma volume and concentration of hemoglobin during a spontaneous remission. Note decrease in plasma volume with rise in concentration of hemoglobin. (Redrawn from Keith, *Am. J. M. Sc.*, 165: 174-184, 1923.)

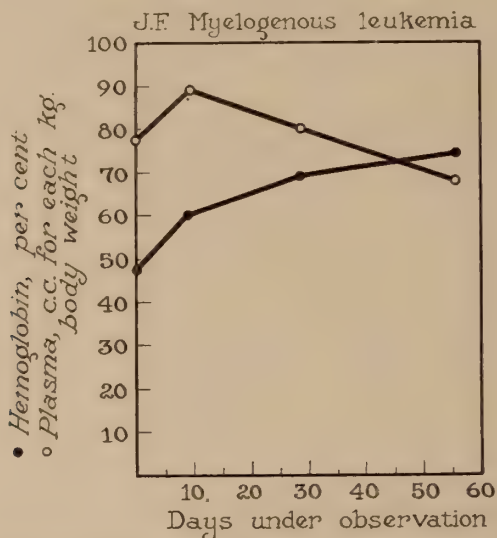


FIG. 7. A case of myelogenous leukemia. Changes in plasma volume and concentration of hemoglobin during recovery from a severe hemorrhage. Note decrease in plasma volume as hemoglobin concentration rose. (Redrawn from Keith, *Am. J. M. Sc.*, 165: 174-184, 1923.)

mentioned previously, in wound shock. It is also diminished when outspoken dehydration is present, for example, after persisting severe vomiting, diarrhea or sweating, and after large areas of the skin have been burned.

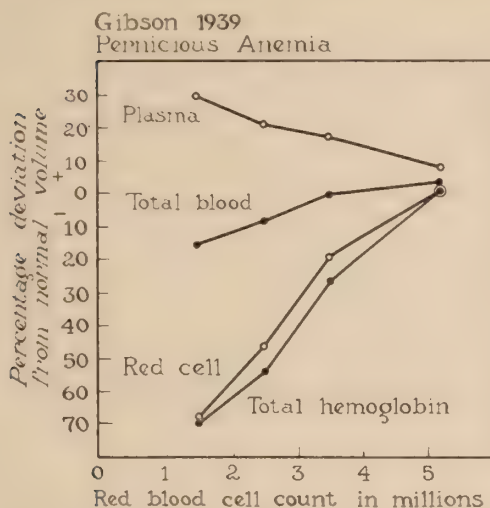


FIG. 8. A case of pernicious anemia. Changes in plasma volume, blood volume, red cell volume and total hemoglobin during a remission due to liver extract therapy. With rise in hemoglobin note decrease in plasma volume. (Redrawn from Gibson, *J. Clin. Investigation*, 18: 401-414, 1939.)

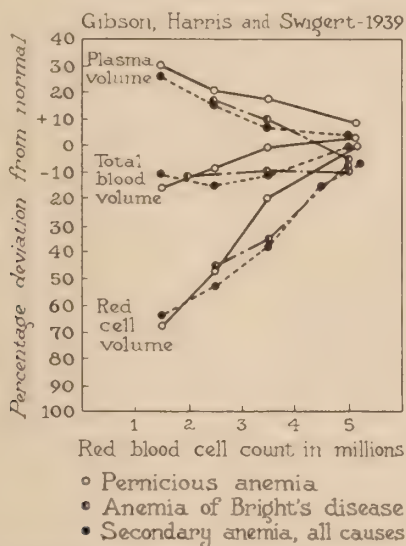


FIG. 9. Changes in plasma volume, blood volume and red cell volume in cases of different types of anemia during a recovery phase. Note decrease in plasma volume with rise in red cell volume. (Redrawn from Gibson, Harris and Swigert, *J. Clin. Investigation*, 18: 621-632, 1939.)

Marriott in 1920 demonstrated by the dye method such a decrease of blood volume in so-called athrepsia of infants. All are agreed that in heart disease associated with severe myocardial failure there is an increase of

both plasma and total blood volume. With restoration of adequate cardiac function the volume returns to the normal level (11). In thyroid disease both oligemia and polyemia are present, the former in myxedema (2, 12, 32) and the latter in some cases of exophthalmic goiter (2, 3, 12). In severe chronic anemias the plasma volume is usually increased (5, 8, 13, 19, 23, 30), but with restoration of erythrocyte volume both plasma and total blood volume approximate the normal (8, 13, 23). In clinical conditions associated with splenomegaly, with or without anemia, the blood volume is variable and when found increased it may not fall after splenectomy (30). Finally all investigators are agreed that in polycythemia vera there is a very large abnormal blood volume, the great increase being due to a remarkable increase in the actual volume of erythrocytes (13, 30).

TABLE 3
Plasma and blood volume in clinical states

	PLASMA VOLUME	BLOOD VOLUME
Wound shock.....	—	—
Dehydration.....	—	—
Myxedema.....	—	—
Hyperthyroidism.....	N	
Congestive heart failure.....	+	+
Pernicious anemia.....	+	N
Secondary anemia.....	+	+
Myelogenous leukemia.....	+	+
Polycythemia vera.....	+	+
	—	+

—, decreased below normal.

+, increased above normal.

The variations of blood volume revealed in the clinical pathologic conditions mentioned in the previous paragraph are not necessarily sudden or rapid; they are in the category of more or less steady states. It should also be emphasized at this point that these variations have been demonstrated by the original dye method as well as by its numerous modifications. In my experience the present methods for indirect estimation of plasma and blood volume have not been so reliable or helpful as they might be in studying rapid or sudden physiologic changes such, for example, as we might expect to occur during marked diuresis. For the accurate study of these possible rapid changes of blood volume, further perfection of technical methods is a worthy objective.

COMMENT

The ideal method of estimating plasma and blood volume has still to be discovered. However, with the methods at present available important changes have been found to occur in several clinical conditions. This is particularly true in wound shock, dehydration and polycythemia and after hemorrhage. Much also has been learned regarding the recovery phases in acute hemorrhage and in different types of anemia. These new facts have led to a better understanding of such physiologic disturbances and hence to the application of beneficial treatment.

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RELATION OF ANOXEMIA TO JAUNDICE IN LOBAR PNEUMONIA¹

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Jaundice in varying degree is a fairly common complication of lobar pneumonia. Thus, in a recent series of 645 consecutive cases at our institution, 42 were complicated by jaundice. Its appearance has usually been accorded serious prognostic import. In the pre-sulfapyridine era the mortality rate for one series of cases with jaundice was 50 per cent as compared with a rate of 18.6 per cent in non-jaundiced cases. This higher mortality rate has led to an active interest in the possible causes of the jaundice.

Many theories have been advanced to explain it. Some of these are obviously untenable, while others, supported by experimental data, appear plausible. It has been attributed variously to gastroduodenitis, to disturbance in intrahepatic circulation, to the breakdown of hemoglobin in red hepatization of the lung, and to hemolysis by pneumococci. All these theories have proved inadequate.

In 1933 Dr. Paul Klemperer and one of the authors (F. K.) studied the histological alterations of the liver in patients dying of lobar pneumonia. Parenchymal degeneration of greater or lesser extent was occasionally noted. A more frequent finding was cholangiolitis. Both of these histologic findings seemed inadequate to explain the icterus, especially since they were observed in non-icteric cases as well. Recently Klemperer and Gerber (1) reviewed the pathologic findings in the liver in cases of lobar pneumonia. As in the study mentioned above they failed to find cholangiolitis consistently enough to attribute jaundice to it alone.

The best explanation yet advanced has been that of Rich (2). The observation had repeatedly been made that in severe anemias, such as pernicious anemia, with consequent tissue anoxia, the liver may manifest central necrosis of varying extent with associated disturbance of function. Moreover, Rich had demonstrated that rats placed in low-oxygen-tension chambers develop a diminished ability to excrete intravenously injected bilirubin, and that the livers of these animals show degeneration of cells in the region of the central veins. He then proposed the theory that the anoxemia which occurs in lobar pneumonia, by its injurious effect on the

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TABLE 1

NUMBER	DATES OF: A. ONSET B. ADMISSION C. TESTS	AGE	DIAGNOSIS AND TYPE*	TEMPERATURE AT: A. ADMISSION B. TESTS	HGB. PER CENT, SAHLI	OXYGEN CON- TENT; OXYGEN CAPACITY	PER CENT SATU- RATION	BILIRUBIN CONTENT—RETENTION		PERTINENT THERAPY
								mgm. per cent	per cent	
1	A. 12/10/38 B. 12/14/38 C. 12/15/38	47	Lobar pneumonia LLL, Pn. Type 6	A. 101 B. 103	80	14.65 16.77	87.4	0.25	3.3	No specific therapy
2	A. 12/15/38 B. 12/19/38 C. 12/20/38	24	Lobar pneumonia RUL, Pn. Type 3	A. 105.6 B. 102	75	14.85 15.88	93.5	0.35	4.8	Had 6 gms. of sulfa- pyridine
3	A. 12/20/38 B. 12/22/38 C. 12/22/38	33	Lobar pneumonia RUL, RLL. Pn. Type 27	A. 103.6 B. 105.6	83	16.62 17.72	93.8	Omitted for extraneous reasons No clinical jaundice	Not done	No specific therapy
4	A. 12/17/38 B. 12/23/38 C. 12/23/38	19	Lobar pneumonia LLL, Left pleural effusion. Pn. Type 8	A. 103.8 B. 101.8	94	19.52 20.81	93.5	1.5	Not done be- cause of jaundice	Had been in oxygen tent for 8 hours
5	A. 12/28/38 B. 1/2/39 C. 1/5/39	50	Lobar pneumonia RUL, Hodgkins Disease. Pn. Type 15	A. 106 B. 100.8	70	13.56 14.20	95.4	0.25	10.0	Had been in oxygen tent for 12 hours. Sulfa- pyridine, 5 gms.
6	A. 1/3/39 B. 1/5/39 C. 1/6/39	14	Lobar pneumonia RLL, Pn. Type 7	A. 104 B. 104.2	80	15.82 16.47	96.1	0.2	5.4	No specific therapy
7	A. 1/6/39 B. 1/8/39 C. 1/9/39	29	Lobar pneumonia LLL, Pn. Types 19-20	A. 101.4 B. 104	85	16.40 17.62	93	0.35	4.35	No specific therapy

8	A. 1/2/39 B. 1/9/39 C. 1/10/39	124	Lobar pneumonia LLL. Urticaria. Sputum not obtained	A. 102 B. 99 4	82	17 85 19 20	93	0 23	2 2	Sulfapyridine, 5 gms.
9	A. 1/7/39 B. 1/11/39 C. 1/12/39	68	Lobar pneumonia RLL. Pn. Type 3	A. 105 2 B. 101 2	97	18 0 20 33	88 6	0 55	3 45	Sulfapyridine, 6 gms.
10	A. 1/7/39 B. 1/12/39 C. 1/13/39	35	Lobar pneumonia LLL. Mitral stenosis. Pn. Type 13	A. 104 B. 99	85	16 35 16 99	96 2	0 48	5 26	Sulfapyridine, 6 gms.
11	A. 1/16/39 B. 1/22/39 C. 1/23/39	37	Lobar pneumonia LLL. Pn. Type 8	A. 105 2 B. 105 2	95	17 40 18 45	93 7	0 50	4 0	No specific therapy
12	A. 1/20/39 B. 1/24/39 C. 1/24/39	19	Lobar pneumonia LLL. Left pleural effusion. Pn. Type 3	A. 103 B. 103	65	14 88 15 27	97 4	0 30	2 43	Sulfapyridine, 6 gms.
13	A. 1/18/39 B. 1/26/39 C. 1/27/39	58	Lobar pneumonia LUL. LLL. Sputum not obtained	A. 102 6 B. 100 8	69	11 81 15 84	73 5	0 60	0	Sulfapyridine, 2 gms.
14	A. 1/24/39 B. 1/28/39 C. 1/28/39	72	Lobar pneumonia LLL. Pn. Type 5	A. 102 B. 100 6	82	17 30 19 08	90 6	0 35	0	Sulfapyridine, 6 gms.
15	A. 1/27/39 B. 1/30/39 C. 1/31/39	41	Lobar pneumonia RLL. Pn. Type 11	A. 104 8 B. 101	75	16 27 16 75	97	0 35	Not done	Sulfapyridine, 4 gms.
16	A. 1/28/39 B. 2/3/39 C. 2/4/39	15	Lobar pneumonia RUL. RLL, RML, LLL. Pn. Type 1	A. 103 B. 99 6	100	19 43 20 9	93	0 38	7 15	Sulfapyridine, 5 gms.
17	A. 2/4/39 B. 2/4/39 C. 2/6/39	41	Lobar pneumonia LUL. Pn. Type 5	A. 104 6 B. 102 8	52	12 02 13 62	88 3	0 65	15 4	Sulfapyridine, 5 gms.

* Blood cultures negative in all instances except: (a) Case 3, in which pneumococcus Type 27 was isolated, (b) cases 10, 25, and 29, in which the blood culture was not done.

TABLE 1—Concluded

NUMBER	DATES OF: A—ONSET B—ADMISSION C—TESTS	AGE	DIAGNOSIS AND TYPE*	TEMPERATURE AT: A—ADMISSION B—TESTS	HGB, PER CENT, SAHLI	OXYGEN CON- TENT: OXYGEN CAPACITY	PER CENT SATU- RATION	BILIRUBIN CONTENT—RETENTION		PERTINENT THERAPY
						<i>vols. per cent</i>		<i>mgm. per cent</i>	<i>per cent</i>	
18	A. 2/6/39 B. 2/8/39 C. 2/9/39	67	Lobar pneumonia LUL, LLL, RLL. Auric- ular fibrillation. Pn. Type 3	A. 103.6 B. 99.6	84	18.18 20.33	89.4	0.85	Not done be- cause of jaundice	Sulfapyridine, 8 gms.
19	A. 2/10/39 B. 2/15/39 C. 2/15/39	36	Lobar pneumonia RLL. No pneumococcus isolated	A. 103.8 B. 103.8	70	15.55 16.40	94.7	0.13	4	No specific therapy
20	A. 2/17/39 B. 2/18/39 C. 2/20/39	26	Lobar pneumonia RLL. Hookworm—second- ary anemia. Pn. Type 5	A. 104 B. 99.6	43	8.15 8.53	95.5	0.40	10	Sulfapyridine, 13 gms.
21	A. 2/12/39 B. 2/18/39 C. 2/20/39	19	Lobar pneumonia LLL. No pneumococcus isolated	A. 102.2 B. 101.6	96	16.69 18.8	88.7	0.25	6.67	No specific therapy
22	A. 2/16/39 B. 2/20/39 C. 2/21/39	64	Lobar pneumonia RUL. Inactive TBC. RUL. Pn. Type 4	A. 102.6 B. 102.4	75	14.58 16.27	90.6	0.8	Not done be- cause of jaundice	No specific therapy
23	A. 3/3/39 B. 3/6/39 C. 3/6/39	16	Lobar pneumonia LUL. Pn. Type 2	A. 105.6 B. 105.6	80	16.34 18.08	90.1	0.55	12.1	No specific therapy
24	A. 3/17/39 B. 3/19/39 C. 3/20/39	15½	Lobar pneumonia RLL, RUL. Pn. Type 1	A. 105.2 B. 98.6	74	14.36 15.49	92.6	0.3	2.3	Sulfapyridine, 10 gms.

25	A. 3/8/39 B. 3/16/39 C. 3/16/39	16	Resolving lobar pneumonia RLL. Pneumococcus not isolated	A. 103 B. 103	75	15.54 16.48	94.5	0.2	7.7	No specific therapy
26	A. 3/9/39 B. 3/13/39 C. 3/14/39	38	Lobar pneumonia LLL. Pn. Type 5	A. 103.4 B. 99.2	78	16.01 16.30	97.7	0.15	2.6	Sulfapyridine, 6 gms.
27	A. 3/18/39 B. 3/21/39 C. 3/22/39	48	Lobar pneumonia RUL. Sputum not obtained	A. 105.2 B. 101.2	76	15.54 16.71	93.	0.47	3.5	Sulfapyridine, 5 gms.
28	A. ? B. 3/24/39 C. 3/25/39	65	Lobar pneumonia RLL. Pn. Type 3	A. 102.2 B. 100.6	76	13.97 16.36	85.4	0.45	5.8	Sulfapyridine, 7 gms.
29	A. 3/11/39 B. 3/19/39 C. 3/20/39	54	Lobar pneumonia RLL. Pneumococcus not isolated	A. 102 B. 102.4	84	17.40 17.91	97.1	0.5	0	No specific therapy

liver, renders this organ less efficient in the excretion of circulating bilirubin, which in many cases of pneumonia is mildly increased. This combination of hyperbilirubinemia and the impaired ability of the liver, damaged by anoxemia, to excrete the pigment efficiently would seem to constitute the essence of the pathological physiology of jaundice complicating lobar pneumonia.

In the absence of a definite pathologic picture to explain the occurrence of jaundice, the functional hypothesis of Rich was deemed worthy of clinical investigation. This study seemed to us to draw additional significance from the possibility that, if the theory could be substantiated clinically, such a functional disturbance might be found to be reversible. Thus, jaundice might be diminished or averted, by the routine administration of oxygen to anoxemic cases.

Method: The series studied by us comprised 29 cases of lobar pneumonia caused by pneumococci of various types. As soon after admission as feasible, usually within a few hours, brachial artery puncture was performed and determination was made of the oxygen content and oxygen carrying capacity of the arterial blood by the method of Van Slyke and Neill (3). In isolated instances where oxygen administration had already been begun, the brachial artery puncture was not done until after discontinuance of oxygen therapy for about a half hour. Immediately following the arterial puncture, the bilirubin excretion test was performed according to the modification by Soffer and Paulson (4) of the original test by Eilbott (5). In this manner the initial blood level of bilirubin was determined, as well as the percentage of retention four hours after intravenous administration of a predetermined amount of this pigment. Five per cent retention of bilirubin after four hours was considered the upper limit of normal. Notation was made, as indicated in the accompanying table, of the type of pneumococci in the sputum, the presence or absence of bacteremia as shown by blood culture, the hemoglobin at the time of the blood determinations, and of therapy such as could conceivably affect the data. Because of its unreliability in the presence of jaundice, the bilirubin excretion test was omitted in instances in which jaundice was demonstrable.

DISCUSSION

As can be seen from reference to Chart 1, there is no obvious correlation in these clinical cases between the degree of anoxemia and the ability of the liver to excrete intravenously injected bilirubin. Case 13, the most anoxemic in the series, with an arterial blood oxygen saturation of only 73.5 per cent showed no bilirubin retention. Case 28, with an oxygen saturation of 85.4 per cent showed retention of 5.8 per cent which represents the slightest impairment, this figure being very close to the upper limit of normal. On the other hand in Case 17, in whom moderate anoxemia existed, the arterial saturation being 88.3 per cent, there was a bilirubin retention of

15.4 per cent. Case 5, who had a bilirubin retention of 10 per cent, had a normal oxygen saturation of 95.4 per cent. In this instance the latter determination was made after oxygen had been given for 12 hours. Although oxygen therapy had been discontinued for one-half hour before arterial blood was drawn, the relationship here is not conclusive. Case 23, showing marked bilirubin retention (12.1 per cent) had only moderate oxygen unsaturation (90.1 per cent). Other cases with impaired bilirubin excretion, less marked than those mentioned above, showed little or no oxygen unsaturation; conversely, cases with more marked anoxemia showed little or no impairment of bilirubin excretion.

Because of the limited number of cases and the failure to demonstrate an obvious correlation between anoxemia and jaundice, trend graphs were constructed plotting the figures for both oxygen content and percentage saturation against blood bilirubin and bilirubin retention. These graphs likewise failed to reveal a relationship between these variables.

It will be noted in table 1 that many of the patients had received initial doses of sulfapyridine before the tests were performed. On the basis of experience with the action of this drug it is believed highly unlikely that the blood determinations were at all influenced by these small initial doses of sulfapyridine.

SUMMARY

1. Twenty-nine cases of lobar pneumonia were studied with a view to determining the relationship, if any, between anoxemia and the occurrence of jaundice in this disease.

2. No obvious relationship could be demonstrated between anoxemia and the presence of jaundice or of disturbance of liver function as determined by the bilirubin excretion test.

3. Construction of trend graphs, plotting oxygen content and percentage saturation against blood bilirubin content and bilirubin retention, likewise failed to uncover any relationships between these factors.

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PLEURAL MESOTHELIOMA

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Few neoplasms have aroused more interest or excited greater differences of opinion than the group of primary neoplasms of the pleura. Since the first description by Wagner (1) in 1870 much has been written regarding their classification, and the different names applied from time to time to the increasing number of cases are indicative of the lack of agreement among authors as to the point of origin of the growth.

The name that has been applied most frequently is "endothelioma," founded upon the belief that lymphatic endothelium was the source of the tumor. The presence within the tumor mass of numerous canalicular formations lined by atypically proliferated cells, which in shape and cytologic features resembled those of the lymphatic endothelium, seemed to justify this view. Borst (2), Hansemann (3), and Ravenna (4), among others, held to this opinion.

However, other experienced pathologists such as Benda (5), Borrmann (6), Krumbein (7), and Kux (8) disagreed, and suggested that the matrix of all pleural tumors should be searched for in the serosal lining cells. Because of the belief prevalent at that time that the lining cells of serosal membranes were derived from celomic epithelium, tumors arising from them were accordingly called "carcinomas."

On the other hand, in other cases on record, canalicular formations suggesting "endothelioma," as well as nests of cells in alveolar arrangement which gave the appearance of an epithelial growth, were both present in the same tumor. For these no better term could be found than the non-committal one of "endothelial carcinoma." This was the conception of Rosembaum (9). Others (Fischer-Wasels (10), Marras (11)) tried to explain this polymorphic picture as resulting from the proliferation of misplaced "rests" of embryonic epithelial cells. However, a different opinion was voiced by Natali (12) who accounted for the presence of both endothelial channels and epithelium-like formations on the basis of atypical proliferation of endothelial cells which, in keeping with their multifarious tendencies, could lead, once stimulated, to cellular growths of heterogenous appearance.

According to D'Alessandro (13), all primary pleural neoplasms, whether originating from the lining cells of the pleura or from the subserous con-

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nective tissue or from the lymphatic endothelium, and regardless of their histology, ought to be regarded as varieties of "sarcoma" because of the mesenchymal nature of all possible sources of the tumor.

According to Ley (14), there are no primary pleural tumors, in the strict meaning of the word; most of the tumors reported as primary in the pleura can be shown on critical examination to be the result of secondary spread from an underlying pulmonary neoplasm. Banyai and Grill's (15) "pleuro-pulmonary" endothelioma lends support to this belief. However, several reports of undoubted primary pleural neoplasms make this view untenable in all but exceptional cases.

Klemperer and Rabin (16), from a critical review of the literature and from a personal study of numerous cases advocated a "unitarian" concept of the origin of pleural neoplasms. Primary pleural neoplasms are divided by them into two main groups, one comprising those which are localized, and the other those involving the entire pleura and usually completely ensheathing the lung. The former comprises many histologic types of benign and malignant cell forms which possess the characteristics of a common origin within the subserous connective tissue. The diffuse form, on the other hand, arises from the surface lining cells—the mesothelium—and should therefore be designated "mesotheliomas." In keeping with the variegated potentialities of mesothelial cells, they have the ability to give rise to growths containing a variety of elements, either epithelial or mesenchymal in type. From this standpoint the wide morphological variations which for so long a time had been a source of endless disputes become easily explained.

Histologic peculiarities of interest in this connection were clearly displayed by an unusual pleural tumor which recently came under observation.

CASE REPORT

History (Adm. 416194; P.M. 10629). B. R., a 60 year old woman, was admitted to The Mount Sinai Hospital on November 3, 1937, with the chief complaint of pain in the left side of the chest, accentuated by breathing. In the last year she had had frequent attacks of palpitation, and for two weeks (following a "cold") had had severe cough accompanied by abundant whitish expectoration, which on one occasion contained blood. Low-grade fever began only a few days before admission.

Examination. On admission the patient was weak and dyspneic. There was flatness to percussion over the entire left side of the chest, and absence of fremitus and breath sounds. The trachea appeared deviated to the right. The heart was not enlarged. However, it appeared displaced, the right border being situated 2 cm. to the right of the midline. The second aortic sound was greater than the second pulmonary sound. Gallop rhythm and pulsus alternans were noted. The blood pressure was 160 systolic and 100 diastolic.

Course. Fluid was aspirated from the left chest but reaccumulated rapidly; its bloody character suggested the existence of a pleural neoplasm, an impression which was confirmed by the results of an exploratory lung aspiration. A small piece of tissue was withdrawn with the aspirating needle and microscopic examination showed

it to be composed of irregular reticulum-like cells and of small round cells with deeply stained nucleus, resembling lymphocytes. Radiotherapy was initiated. However, the course was rapidly downhill, the patient became progressively weaker, auricular flutter developed and she expired on December 23, 1937.

*Necropsy findings.*² The body was that of a well developed, small, thin woman of about 60 years of age. The mucous membranes were pale and the skin had a peculiar dusky color; however, there were no signs of cyanosis and the fingers and toes showed no clubbing. A small pedunculated polyp of the skin was seen on the lower left abdominal wall.

Chest. Except for a few easily broken fibrous adhesions, the right pleural cavity was clear. The left pleural space contained an abundance of serous blood-tinged fluid and in addition a huge nodular mass (fig. 1). The latter almost entirely encased the left lung which was compressed and collapsed to about one-half its usual volume (fig. 2). The tumor was firmly adherent to the parietal pleura and somewhat less firmly bound to the visceral pleura. On the diaphragmatic portion of the former the tumor appeared in the form of several discrete polypoid masses, varying from 2 to 6 cm. in diameter. Over the anterolateral aspect of the left upper lobe the continuity of the enveloping mass was broken; here the visceral pleura of the surface of the lung was visible over a roughly circular area 6 cm. in diameter. However, at the extreme apex of the lobe a spherical cherry-sized nodule of tumor tissue, densely adherent to the visceral pleura, was present. On the mediastinal surface the tumor mass was about 2.5 cm. thick and extended to the parietal pericardium. The tumor itself had a uniformly firm, though not hard, consistence, and both externally and on the cut surface showed a homogeneous, gray-yellow, waxy color. Except for the upper portion of the upper lobe and most of the lower lobe, which were encased and largely penetrated by the above-described mass, there was no other discrete tumor tissue within the left lung resembling the external tumor mass. In the tumor-free areas the pulmonary parenchyma was soft, somewhat dry, and pinkish in color, with the usual anthracotic markings. This was also the appearance of the right lung which on the most careful examination did not reveal the presence of any area having the semblance of tumor tissue. The only abnormal findings offered by the right lung were two small subpleural calcified nodules, one in the axillary and the other in the paravertebral region. The trachea as well as the bronchi showed no unusual features. There was moderate arteriosclerosis of the pulmonic arteries; the veins seemed to be intact. The tracheobronchial lymph nodes, which were somewhat anthracotic, did not show any involvement by tumor, being small and of the usual soft consistence. The normal appearance of the superior mediastinum was unchanged as was the mutual relationship of its structures. No grossly recognizable thymic tissue remained and the great vessels at the base of the heart were covered by a small quantity of yellow fat. The parietal pericardium was densely adherent to the mediastinal pleura as described above. The internal surface of the pericardium, however, was clear and smooth, and the sac contained a moderate amount of clear yellow fluid. There was no evidence of tumor in the myocardium which everywhere appeared to be firm in consistence and red in color. The heart weighed 295 grams. There was noted calcification of the mitral valve ring, hypertrophy of the right and left ventricles, dilatation of the right auricle and ventricle, and coronary arteriosclerosis.

Abdomen. No fluid was found on opening the abdominal cavity; both parietal and visceral peritoneum were perfectly smooth and glistening everywhere. The dome of the diaphragm rested at the fourth intercostal space on the right side and at the fifth on the left side. The liver was very small, weighing 860 grams. It was con-

² Necropsy was performed on December 23, 1937 by Dr. Plaut. Because of limited permission the organs were removed through an abdominal incision.

gested and in a rather limited area showed three or four subcapsular nodules, about 2 mm. in diameter, which projected a few millimeters into the liver parenchyma and had a homogeneous pale tan appearance. The spleen, which was also congested, displayed prominent trabeculation and increased size of follicles; it weighed 125 grams. Except for the presence of a multiloculated thin-walled cyst, about 2 cm. to the left of its head, the structure of the pancreas was not unusual. The esophagus and stomach showed no abnormalities. The mucosa of the small intestine was slightly injected, and a firm, submucosal, sessile, polypoid mass, 2 mm. wide, was found in the ileum. A similar polypoid structure, somewhat larger, was detected in the cecum, 2 cm. from the ileocecal valve. This was flattened and contained a central ulcerated portion which was white in contrast to the rest of the mass. The mass itself was darker than the surrounding mucosa and had a blue-green cast. Both kidneys were similar in size, shape, and color; together they weighed 285 grams. Both had a dark red color and their surfaces were for the most part smooth except for a small number of stellate depressed and puckered scars. The architecture of both the cortex and the medulla was well preserved; however, the corticomedullary demarcation was slightly indefinite. In the right kidney there were in addition several cortical cysts. The pelvis and ureters were not unusual but the mucosa of the bladder showed some congestion. The uterus was small; on its posterior surface lay a cherry-sized nodule which on section had the whorl-like fibrous appearance of a fibromyoma. The cervical canal showed several Nabothian cysts and fibroadenomatous polyps. Similar polypoid masses were also present in the uterine body arising in the endometrium. The structure of the ovaries was not unusual.

Throughout the body the lymph nodes were not found enlarged or otherwise conspicuous.

Microscopic anatomy. Sections were taken from various portions of the pleural tumor, including the infiltrated lung. In order that a detailed study might be made, numerous sections were also taken from the principal organs of the body and special attention was directed to the liver, pancreas, intestines, and genital organs which at the autopsy had displayed some macroscopic abnormalities. The material was fixed in Bouin solution and 10 per cent formaldehyde, and was embedded in paraffin. The sections were stained with hematoxylin and eosin and with Van Gieson hematoxylin stains. The silver impregnation method of Bielschowsky-Maresch for the precollagenous connective tissue and the Sudan stain on frozen sections were also employed.

The tiny subcapsular nodules that were found in the markedly congested liver appeared to be in no way related to the tumor mass of the chest on microscopic examination, but corresponded to "bile duct adenoma-like formations." A similar adenomatous structure was displayed by the pancreatic cyst which clearly showed a cuboidal epithelial cell lining and granular eosinophilic contents. The polyp-like vegetation found in the ileum appeared to be due to a submucosal nodule which projected into its lumen. This nodule was composed of a hyalin homogeneous and structureless material about which there were several foreign-body giant cells and a few scattered collections of lymphocytes and plasma cells. This formation was completely surrounded by a mantle of dense, somewhat cellular, fibrous connective tissue. The structure of the polypoid mass found in the cecum was different. This seemed to result from a projection into the lumen, a redundancy of the mucosa and inner muscle layer. At one point the raised mucosa showed an invagination whose *cul-de-sac* contained a granular pink-brown structureless material. The impression gained at the autopsy table of the uterine findings was found correct at the examination of the corresponding microscopic sections. The skin nodule was a typical lipoma.

Since no doubt existed as to the secondary nature of the scattered discrete tumor

areas found in the left lung, and since the existence of any other malignant tumor in the body had been excluded by gross and microscopic examination, the pleural neoplasm was regarded as having originated in that site. The histology supported this view.

Tumor of the pleura. The parietal pleural surface was irregularly thickened. In places the thickening appeared to be due to the presence of densely packed bundles of hyaline fibrous connective tissue. Elsewhere a loose appearance was predominant and between the meshes of intersecting connective fibres lay in great number dark-staining cells resembling lymphocytes. Upon the pleural surface areas were encountered which showed a rather well preserved mesothelial lining. It consisted of rows of monostratified cells which were uniformly flattened and somewhat spindle-shaped, with scanty cytoplasm and large oval nuclei. In other areas these cells, although still appearing regularly disposed in a single layer, seemed to be larger and exhibited a tendency to cuboidal shape. Areas were encountered finally which displayed undoubted signs of atypical mesothelial cell proliferation, either in the form of regularly superimposed layers of cells or in small collections which projected above the pleural space in the form of microscopic vegetations. Under higher magnification these atypically proliferated mesothelial cells were of various shapes, oval in places and rounded in others, often revealing large cytoplasmic processes which had a tendency to fuse with similar processes of other adjacent cells. Quite uniform on the other hand was the appearance of the nuclei which, round or oval in shape, showed a sharp limiting membrane and a scanty chromatin network containing at times small nucleoli. The surrounding cytoplasm was homogeneous, dark, and compact.

Strands of dense connective tissue extended from the thickened pleura and penetrated in a spreading manner into the underlying tumor tissue. Some of these trabeculae did not show any cellular lining. Others showed at the periphery a more or less continuous lining of cells, either mono- or pluristratified, which displayed the cytologic characteristics of the pleural mesothelial cells described above.

Within the loculi formed by the intersecting fibrous trabeculae lay masses of cells and extremely numerous blood capillaries (fig. 3). These cells under higher magnification revealed distinct differences in size, shape, and cytologic characteristics, so that among them three different types, varying in proportion in the different sections, could easily be recognized:

(a) Round cells with a narrow zone of cytoplasm and very dark nuclei, resembling in all respects lymphocytic cells. These lymphocyte-like cells varied greatly both in size and cytologic characteristics. Some, very large, with fine nuclear chromatin structure and two or more nucleoli, reminded one very much of lymphoblasts of the lymphatic tissue. Others resembled mesolymphocytes because of the clearer blue-staining cytoplasm and the coarser nuclear structure. Others, finally, had all the appearances of the small lymphocyte (fig. 6).

(b) Large cells uniformly distributed either singly or in loosely connected groups. Prominent among these elements were round and oval-shaped cells, with short drawn-out acidophil cytoplasmic processes. Their nuclei were oval, with enfolded nuclear membrane and a scanty fine chromatin network containing at times small nucleoli. Often two nuclei were evident. Fat contents in the form of fine droplets were revealed in the cytoplasm by the Sudan stain (fig. 5).

(c) Cells resembling the latter, but much larger, with several protoplasmic processes, bizarre huge nuclei, and occasionally multinucleated giant cells.

In some areas the dark lymphocyte-like cells predominated and only a few of the large type were seen. In other areas the large cells were prominent and took the form of a pale-staining reticulum cell.

Furthermore, in addition to a moderate number of neutrophilic leucocytes,

spindle-shaped elements with elongated vesicular nuclei were encountered here and there, irregularly scattered, singly or in groups. These elements, easily identified as fibroblasts, were chiefly seen attached to the walls of the blood vessels which, extremely numerous, completed the histologic picture of the tumor.

The vessels—in longitudinal and cross section—were mostly blood capillaries and only a few larger veins were present here and there. Their walls were in general very thin, appearing to be composed of a single endothelial lining, lying upon a fine fibrous membrane. This was the predominant appearance; however, quite frequently, vessels were seen which showed a thicker fibrous membrane with corresponding narrowing of the lumen. Through increasing thickening of the fibrous outer walls, stages were finally reached in which the normal structure of a blood vessel appeared to be either completely or almost completely lost, giving place to brightly-stained eosinophilic masses, round or oval in shape, composed of hyalin fibrous tissue arranged in a somewhat concentric manner.

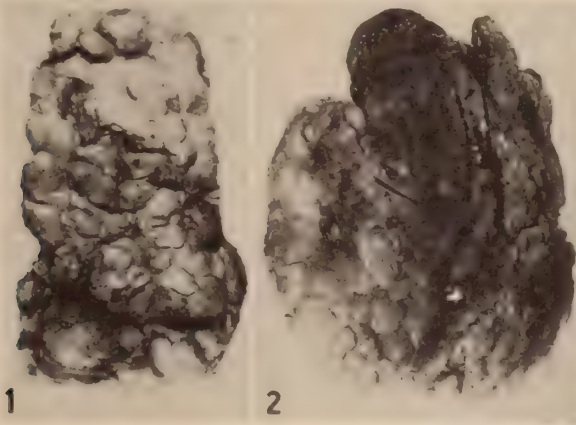


FIG. 1. Inner aspect of portion of parietal pleura showing diffuse, nodular tumor infiltration.

FIG. 2. Tumor infiltration of visceral pleura partially encasing the left lung.

In most of the slides examined no intercellular material was seen, the cells appearing closely approximated. However, in sections impregnated with silver according to the Bielschowsky-Maresch method, the areas in which the large pale-staining cells were prominent clearly demonstrated the presence of an abundant network of fibres which surrounded almost every cellular element.

These features of the neoplasm were exactly reproduced by the areas in the left lung which had appeared grossly to be infiltrated by the tumor. A network of fibrous trabeculae was likewise present everywhere and within its loculi both the large reticulum-cell-like elements and the lymphocyte-like cells, together with occasional multinucleated giant cells, were clearly demonstrated. The lymphocyte-like cells seemed to predominate although the larger elements were very numerous. Sections from the lung, perhaps better even than the pleural sections, showed the close relationship which probably existed between the atypically proliferated mesothelial cells and the other cellular elements of which the growth was composed. Groups of mesothelial cells lining the trabeculae were clearly seen springing from the fibrous walls to spread either singly or in loosely connected groups within the surrounding cellular matrix of the tumor (fig. 4). The relationship was further suggested by the close

resemblance that the nuclei of the atypically proliferated mesothelial cells bore to the nuclei of both the largest lymphocyte-like cells and of the elements having the appearance of reticulum cells; all showed the presence of nucleoli and fine chromatin structure.

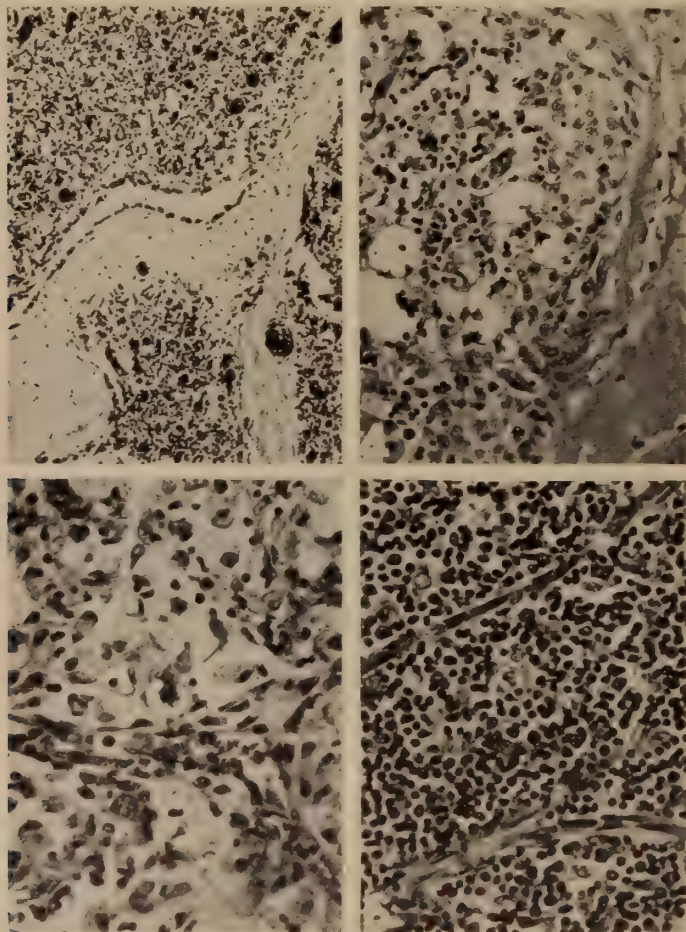


FIG. 3 (top left). Area of tumor showing formation of cleft-like space lined by mesothelial cells partially supported by fibrous tissue ($\times 80$).

FIG. 4 (top right). Area of tumor showing proliferation of cells intermediate in differentiation between mesothelial cells and elements resembling reticulum cells ($\times 180$).

FIG. 5 (bottom left). Fat containing elements with appearances of histiocytes seen in high magnification ($\times 200$).

FIG. 6 (bottom right). Area of tumor showing predominant lymphocyte-like differentiation of cells ($\times 200$).

Between the areas of lung tissue infiltrated by the tumor were seen areas of emphysema alternating with more extensive atelectasis and foci of chronic organizing pneumonia. The blood vessels showed intimal fibrous thickening; dense mantles of fibrous connective tissue, densely infiltrated by lympho-monocytic cells, were evident around the small and medium-sized bronchi.

A similar picture of emphysema, atelectasis, and focal chronic pneumonia, was

displayed by the right lung, which, however, on the most careful examination failed to show any neoplastic involvement.

The numerous hilar lymph nodes examined were also free of tumor cells but showed much fibrosis and huge deposits of anthracotic pigment. Neoplastic involvement was unexpectedly found in a periportal lymph node which because of its gross enlargement had been subjected to microscopic examination. On microscopic examination various portions of the gland showed islets of neoplastic cells, for the most part located within the sinuses. The arrangement of the cells varied greatly. There were areas in which the cells were closely approximated with scant intercellular material. In places the cells lay in nests forming an alveolar arrangement which gave the appearance of an epithelial growth. In other places they were disposed in rows with a tendency to form intersecting trabeculae. Under higher power the histologic resemblance of these elements to the mesothelial cells of the primary pleural tumor appeared unquestionable. The cells varied considerably in size and shape, flattened in some places, and rounded in others. The size of the nuclei was likewise irregular. The larger of them possessed evident nucleoli, a sharp limiting membrane, and a loose chromatin network. Many of the cells contained two or more nuclei, and possessed large eosinophilic cytoplasmic processes which showed a tendency to fuse with similar processes of other adjacent cells.

COMMENT

In summary, this case belongs to the group of diffuse pleural neoplasms whose pleural origin is beyond question. Throughout the entire clinical course of the illness there was no suspicion of newgrowth arising in any other region of the body, and at autopsy no other growth was found that could possibly have been considered as primary. The histology supported this view.

Outstanding features of the tumor were:

(a) Strands of dense connective tissue growing inward from the thickened pleura, and often lined by a discontinuous layer of mesothelial cells in atypical proliferation.

(b) Exceedingly numerous blood capillaries, with marked fibrous thickening of their walls, resulting in the formation of large hyalin bodies.

(c) Masses of peculiar cells within the loculi formed by the intersecting fibrous trabeculae.

A discussion of the cell types is of importance in understanding the genesis of the neoplasm. Prominent among them were large cells with pale nuclei which both in their morphology and in their arrangement bore close resemblance to reticulum cells whose forerunners are the mesoblasts of embryonic connective tissue. Further support for this view is found in the fact that some of these cells showed lipid storage. That this was an expression of true storage rather than of cellular damage is indicated by the apparently good state of preservation of the involved elements.

The presence of a thick network of argentaffin fibres in close relation with these cells gave further evidence for their reticulum cell nature. This was brought out in sections stained with special methods. No intercellular material could be seen where the cells were more abundant and

apparently more immature. On the other hand, where a loose appearance was prevalent with a tendency of the proliferating cells to arrange themselves in intersecting rows, almost every cell appeared surrounded by a thick network of argentaffin fibres. Roulet (21) similarly recognized among typical tumors arising from reticulum cells two varieties, one characterized by the presence of exceedingly numerous argentaffin fibres in close relation with the proliferated cells, the other, poorer in fibres and chiefly composed of large cells fused together with loss of demarcation. To the former group, in his opinion, belonged the more mature tumor types, to the latter the more immature ones. Grynfeldt (22) accepted this subdivision and applied it to his own mesenchymal tumors, dividing them into "fibrillogenous" and "afibrillogenous" varieties. In the case herein reported both fibrillogenous and afibrillogenous areas were found. In agreement with the views of Roulet and Grynfeldt they were thought to correspond with different stages of maturity of the developing cells.

It is therefore justifiable to conclude that the neoplasm consists of relatively undifferentiated elements, the microscopic appearance of which conforms with that of the reticulum cells derived from embryonic connective tissue.

There is some doubt concerning the nature and source of the lymphocyte-like cells which were often so numerous in the tumor as to predominate over the larger reticulum cell-like elements. These dark-stained round elements paralleled the various stages of maturation of the blood lymphocytes. In general they were not found to lie in particular proximity to blood vessels; moreover, the latter were not congested, nor did they contain many lymphocytes. It is impossible, therefore, to apply in this case, the hypothesis of an extravasation of lymphocytes from the blood as Schminke (23) first, then Derigs (24) assumed to explain the huge masses of lymphocytic cells which, in addition to elements of a more particular character, were present in their so-called "lympho-epithelial" tumors. More plausible is the opinion of Segre (25) who, discussing a reticulum cell tumor of the lymph nodes in which there were exceptionally numerous young lymphocytic cells, advanced the belief that both reticulum cells and lymphocytes arose independently from a highly undifferentiated ancestral cell able to give rise on the one hand to reticulum cells and on the other to lymphocytic cells. Instances of neoplasms in support of this hypothesis are quite numerous. Under the title "Kombinierte Formen" Roulet (21) describes reticulum cell tumors of different organs in which either leukemic or lymphogranuloma-like features were concomitant findings. In lymph nodes, similar observations were reported by Vecchi (26) and by Montpellier, Manceaux, and Assan (27), all authors agreeing in the belief of an atypical growth evolving in more than one direction from an undifferentiated stem cell.

Accordingly Oberling (28) and later Craciun and Ursu (29) divided

reticulum cell tumors of bone marrow and lymph nodes, respectively, into three chief groups. To the first group they assigned the undifferentiated forms composed of elements which maintain the appearance of the parent stem cell. The second group comprised the more differentiated types including elements more mature morphologically and equipped with some of the normal functions of cells of this system (phagocytosis). To the third group, belonged those tumors displaying hematic cell differentiation, either towards the myelogenous series (reticulum cell myelosarcomas) or toward the lymphocytic series (reticulum cell lymphosarcomas).

If one attempts to explain in the case reported herein the association of three different types of cellular elements—the mesothelial, the lymphocyte-like, and the reticulum cell-like forms, the possibility of a common source or at any rate of a close interrelationship of these seemingly heterogeneous cells must be considered. Histologic evidence to support this belief was found, both in the primary tumor and in the metastatic nodules of the lung. Groups of atypical mesothelial cells were frequently seen to separate from the fibrous trabeculae and to invade the surrounding matrix of the tumor. The nuclei of the mesothelial cells bore close resemblance to the nuclei of the larger lymphocyte-like cells and of the elements having the appearance of reticulum cells, suggesting an origin of all these cells from a common neoplastic parent mesothelial cell. Of course, one realizes that histologic resemblances are not conclusive proof of actual transformation of one cell type into another. However, the transformation of mesothelium into mesenchymal cells has been experimentally demonstrated by tissue cultures. This observation lends support to this interpretation of the histogenesis of these tumor cells.

SUMMARY

A case is reported of diffuse neoplasm of the pleura arising from the mesothelial lining cells. The complex structure of the tumor, chiefly composed of lipophagic reticulum cell-like elements and of cells resembling lymphocytes in different phases of development, is explained on the basis of the multiple developmental potentiality of the mesoderm comprising the coelomic "mesothelium."

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ACUTE PERFORATIONS OF THE GASTROINTESTINAL TRACT DURING HOSPITAL OBSERVATION¹

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It is customary to classify disease entities as medical or surgical, depending upon whether operative or non-operative therapy is employed. There is, however, a large group of cases in which certain complications of the original medical entity become urgently surgical. To meet this need for joint surveillance the present tendency in well organized hospitals is to have a liaison between the medical and surgical services either by frequent consultations or by the assignment of a member of the surgical service to the medical wards, and *vice versa*. It is a common experience to find surgical conditions inadvertently admitted to the medical wards. Appendicitis and cholecystitis are the most common and then again acute surgical accidents may occur in the course of medical therapy. Perforation of a hollow viscus into the peritoneal cavity as the result of ulceration of either a benign or malignant lesion of the gastrointestinal tract is a common example.

Numerous circumstances tend to obscure accurate and immediate diagnosis and to delay surgical intervention. In contrast to the patient brought into the hospital, usually by ambulance, with a perforation of the gastrointestinal tract most commonly due to an ulcer or carcinoma of the stomach or duodenum in which the clinical picture is so clear that the youngest member of the interne staff can readily make the diagnosis, this very lesion when encountered in the medical wards offers a much more serious diagnostic problem. The patient admitted for in-bed treatment of a peptic ulcer usually has a penetrating lesion with severe pain, often requiring hypnotics; frequently upper abdominal tenderness and some spasticity is present. It often requires fine clinical judgment to recognize the additional changes occurring with perforation. We have become increasingly concerned with the frequency of gastrointestinal perforations occurring spontaneously on the medical wards of the hospital and feel that a review of such cases will be helpful in drawing attention to 1) the major groups in which perforations spontaneously occur; 2) the various factors which seemingly contribute to or initiate this accident; 3) the factors which apparently alter the prognosis (x-ray perforation); 4) diagnostic difficulties

¹ The authors wish to express their thanks to the chiefs of the services from which this material has gathered.

and the clinical picture of perforations occurring during hospital residence as contrasted with those occurring prior to admission, and finally 5) to the significance of this condition so that prompt action may be taken insuring better results.

Diagnostic difficulty is not confined to ulcer, for free perforations of the colon may be equally difficult to recognize. In ulcerative colitis of long standing during an acute exacerbation, the general abdominal distention and tenderness associated with this condition along with the general toxic and debilitated state of the patient at times makes diagnosis puzzling. In this condition, particularly, pericolic abscess formation and peritonitis unassociated with actual perforation simulate one another so closely as to make an accurate differential diagnosis at times impossible.

We have reviewed the case histories of all perforations of the gastrointestinal tract occurring on the ward service of the hospital between the years 1926 and 1941 and have selected for review and discussion those cases, twenty-two in number, in which the perforation could be established as having taken place during hospital residence. Lesions of the stomach and duodenum comprised more than one-half of the total number, thirteen in all. Perforation of the ileum occurred in two cases. The colon was the seat of perforation in seven instances. We have eliminated instrumental perforations of the esophagus and rectum inasmuch as we feel these lesions are a distinct entity in themselves. The therapy, and their diagnostic features have been amply covered by Touroff (1) and Sallick (2). Nor have we included perforations of the appendix and gall bladder which have undoubtedly occurred but which would have been difficult or impossible of verification. We have also omitted a very few cases of typhoid perforation.

Gastric and Duodenal Perforations. The site of perforation in this group (Table I) was duodenal in eight instances, at the pylorus in one, and of the stomach in four. Of the last group, one patient returned with a definite carcinoma of the stomach, another was proven to be carcinoma by resection, and a third suspected on the basis of operative findings. While the incidence of ulcer in general is normally much larger in men and perforation correspondingly frequent, this series includes only one woman. The youngest patient was 28 years old, and the oldest patient was a woman 74 years of age. In all these cases with but two exceptions (one, a case of generalized periarteritis nodosa in which perforation occurred 48 days after admission, and the other, a diabetic admitted for gangrene of a toe in which perforation entirely unsuspected occurred approximately one month after admission), the patients were admitted to the medical wards with complaints referable to the upper digestive tract and were treated as ulcer or carcinoma suspects. In two cases a suspicion of cholecystitis was entertained. In the majority of cases perforation occurred reasonably soon after hospital admission, particularly in the group with symptoms classical

of ulcer. In two cases perforation occurred one day after admission; in four, two and three days after entrance; in one, four days after admission; in three, approximately one week after admission; in one, eighteen days after admission; and the two cases in which the diagnosis of ulcer was not entertained, over a month after admission. This would tend to emphasize the fact that the symptoms from which this group were suffering when first seen were in reality symptoms of impending perforation rather than penetration. It is of interest to note in passing the marked difference in time of perforation of the ulcer group as opposed to the colon group in which perforation took place at a relatively much later date. This will be further discussed in analysing the colonic material. In the three cases deemed to be neoplastic, perforation occurred two, four and seven days after hospital residence.

Symptomatology. We have attempted, insofar as this was possible, to differentiate between the prodromatal symptoms of perforation and those of the actual perforation. It would seem as though the in-bed patient would lend himself ideally to this consideration. Practically, this is not always the case. Some degree of pain of clinical significance was present before perforation in seven patients; in two, the pain was mild. In two cases there were no symptoms referable to the gastrointestinal tract, one of these patients dying with a perforation completely undiagnosed and unsuspected, the other giving symptoms only three hours before demise, the clinical picture being obscured by diffuse arterial disease (periarteritis nodosa). In one case the picture was entirely altered by a recent laparotomy for a perforated ulcer which was sutured successfully, to be followed by another entirely independent perforation six days after the first operation. This case is noteworthy in that the diagnosis was correctly made, the patient was reoperated upon and recovered. With certain exceptions, the symptoms of actual perforation, while not nearly so dramatic as in those patients with perforations before admission, were nevertheless fairly characteristic. Pain was the outstanding symptom except in one patient. It was not always easy to appreciate the increase of pain accompanying the perforation nor to be sure that perforation had not actually occurred sometime before the symptoms were first appreciated by either the house or attending staffs. A patient in the hospital with a diagnosis of ulcer suspected or established, who is having more or less regular pain, may have a perforation with an increase in symptoms which are considered to be only a more severe exacerbation of his presenting clinical picture. The pain was usually epigastric in location, in some cases radiating to the right flank or shoulder. Right upper quadrant pain was not infrequent. In two cases the pain was accompanied by nausea and vomiting.

Signs. Rigidity and tenderness were the most frequent physical findings. These occurred at some time following perforation in all but one

ADMISSION NUMBER	AGE	ADMISSION DIAGNOSIS	PROBABLE TIME OF PERF. AFTER ADMISSION	PRODROMATA	INITIAL SYMPTOMS OF PERFORATION	SIGNS OF PERFORATION
416427 (male)	47	Psychoneurosis; peptic ulcer	2 days	Epigastric pain	Pain, not perceptibly increased for sev. hrs.	Rigidity (late) not marked;
320516 (male)	69	Carcinoma of stomach; pyloric obstruction	18 days		Epigastric pain; 2 attacks	Epigastric and tenderness a
334080 (male)	48	Penetrating peptic ulcer? Cholecystitis?	2 days	Very mild abdominal pain	Pain, severe in R.U.Q. and epigastrium	Mild shock, sp tenderness
306987 (male)	51	Pyloric stenosis; duodenal ulcer	3 days	Epigastric pain	Increase in pain; vomiting	Collapse, cyanosis, tender
332489 (male)	40	Peptic ulcer	1 day	Epigastric pain	Sudden severe R.U.Q. pain	R.U.Q. and rigidity
365916 (male)	51	Cholecystitis? Peptic ulcer?	6 days	Dizziness	Sudden severe upper abdominal pain radiating to left shoulder	Rigidity and most marked
307445 (male)	61	Penetrating peptic ulcer	2 days	Severe abdominal pain	Severe pain awakening him from sound sleep	General abdominal rigidity and tenderness
318744 (male)	28	Perforating ulcer	6 days	Entered with perforated ulcer which was sutured	Severe abdominal pain	Spasticity of
334926 (male)	50	Penetrating duodenal ulcer	1 day	Constant epigastric pain	Severe pain radiating to right flank	Tenderness upper abdominal
355151 (male)	58	Pyloric stenosis due to neoplasm or ulcer	7 days		Abdominal pain	Upper abdominal lower abdominal tenderness; rt. side
374154 (male)	34	Carcinoma of stomach	4 days	None	Pain, shock, air hunger	Tenderness; rigidity
353838 (male)	37	Periarteritis nodosa (final diagnosis)	41 days	None	Abdominal pain	Rigidity; tenderness; rt. lower
450291 (female)	74	Diabetic gangrene	Over 1 month	None	None	None except temperature

of stomach and duodenum

MADE: DATE	CONFIRMATORY EVIDENCE OF PERFORATION	PRECIPITAT- ING FACTORS	THERAPY	ESTIMATED TIME FROM PERFORA- TION TO OPERATION	OPERATIVE FINDINGS	RESULT	POST-MORTEM FINDINGS
12 hrs. probable on	X-ray and abd. puncture	G.I. x-ray during (?) perforation	Operation: suture of peptic ulcer	12 hrs. ?	Free air, barium in peritoneal cavity, 6 mm. perf. ant. wall duodenum	Ceased	Generalized peri- tonitis cause of death; perito- nitis, broncho- pneumonia
ulcer or na	Fluid and air under diaphragm	Gastric lavage	Operation: suture of ulcer	12-17 hrs. ?	Large perf. ant. wall duode- num ulcer) large amounts free fluid	Ceased	Generalized peri- tonitis, sub- phrenic abscess
ulcer?	X-ray for free air negative	None	Operation: suture of ulcer	1½ hrs.	Ant. wall duo- denum perfora- tion free fluid	Well	
for 7 y diag-	X-ray—free air un- der both leaves of diaphragm	G.I. x-ray	Conservative	No opera- tion; con- dition too grave		Ceased	Generalized acute purulent
diag-	No free air x-ray	None	Operation	2 hrs.	Ant. duod. wall perf.	Well	
diag-	Free air under dia- phragm	G.I. x-ray 3 hrs. later	Operation	1½ hrs.	Large perf. gas- tric ulcer	Ceased	Paralytic ileus diphtheritic ileitis
diag-	X-ray—free air under both leaves of dia- phragm	None	Operation	1½ hrs.	Gastric ulcer	Well	Note readmis- sion later as gastric carci- noma
ation of tion of	Elevated temp. leucocytosis abd. puncture	None	Operation	5½ hrs.	Old suture line intact new perf. over 1" away	Well	
diag-	None	None	Operation: sub-total gastrectomy	1½ hrs.	Large duod. post. wall perf.; much fluid in peri- toneum	Well	
hrs		Gastric lavage	Operation: closure and button gas- troenteros- tomy	12-14 hrs.	2½ liters of fluid in peritoneum; ten cent sized perf. ant. surf. pylorus(neo- plasm)	Ceased	No P.M.
diag-	None	None	Operation: gastrectomy	2 hrs.	Carcinoma of stomach	Well	
diag-				Died in 3 hrs.		Ceased	Perf. pep. ulcer in pt. with exten. periar- teritis nodosa
	None	None	None			Ceased	Perf. of pep. ul- cer on ant. wall of 1st por- tion of duod., with diffuse peritonitis

Resumé of relevant data in

ADMISSION NUMBER	AGE	ADMISSION DIAGNOSIS	PROBABLE TIME OF PERF. AFTER ADM.	PRODROMATA	INITIAL SYMPTOMS OF PERFORATION	SIGNS OF PERFORATION
452065 (female)	67	Possible intestinal obstruction	3 weeks	None	Fever and generalized abdominal pain	Abdominal tenderness; distention
437078 (male)	48	Bronchiectasis R.L.L. and L.L.L.	8 days	None	Pain in R.U.Q.	Abdominal tenderness; rigidity in upper right quadrant

Resumé of relevant

ADMISSION NUMBER	AGE	ADMISSION DIAGNOSIS	PROBABLE TIME OF PERF. AFTER ADM.	PRODROMATA	INITIAL SYMPTOMS OF PERFORATION	SIGNS OF PERFORATION
297623 (female)	18	Ulcerative colitis	35 days		Pain	Tenderness; rebound tenderness
308735 (female)	22	Ulcerative colitis	32 days	None	Severe R.L.Q. pain	Tenderness; no rebound
384724 (female)	17	Ulcerative colitis	?		Abdominal cramps	Tenderness; rebound tenderness
311799 (female)	20	Ulcerative colitis	58 days	Abd. soreness	Abdominal pain	Tenderness; marked abdominal distention; slight rigidity
365694 (male)	28	Amoebic colitis	35 days (circa)	Diarrhea; abd. pain	R.L.Q. pain; epigastric distention	L.L.Q. marked tend.
309468 (male)	20	Hirschsprung's cong. dil. colon	4 days	None	Distention; abdominal pain; shock	Marked distention; obliterated ileocecal junction
446859 (male)	33	Ulcerative colitis	7 weeks	None	Pain and fever but no increase from previous course	

Lesions of the small intestine

CASES NOT T	CONFIRMATORY EVIDENCE OF PERFORATION	PRECIPITATING FACTORS	THERAPY	ESTIMATED TIME FROM PERFORATION TO OPERATION	OPERATIVE FINDINGS	RESULT	POST-MORTEM FINDINGS
1	None	None	None			Ceased	Decubitus ulcer formation in ileum and spontaneous perforation caused by large gall-stone
2	None	None	Suture of perforation	14 hours	Perforation of ileum and peritonitis	Ceased	Lymphosarcoma of terminal ileum with perforation (sutured) and generalized peritonitis

Lesions of the colon

CASES NOT T	CONFIRMATORY EVIDENCE OF PERFORATION	PRECIPITATING FACTORS	THERAPY	ESTIMATED TIME FROM PERFORATION TO OPERATION	OPERATIVE FINDINGS	RESULT	POST-MORTEM FINDINGS
1	None	None	Ileostomy with drainage	1 day	Perforation in ulcerative colitis; fecal peritonitis	Ceased	Perf. lesion of caecum; fecal peritonitis
2	None	None				Ceased	Perforation of caecum. <i>Note:</i> this patient went on to perforation in spite of ileostomy 6 days earlier
3	None	None	Ileostomy	?	Diffuse peritonitis	Ceased	Perf. at recto-sigmoid junction
4	None	None	None			Ceased	Acute diffuse fibrino purulent peritonitis; ulcer. colitis with perf. at splenic flexure
5	Free air under diaphragm	None	Transverse colostomy	28 days	Large cavity entered (transverse colon)	Ceased	Severe ulcerative colitis; perf. transverse colon
6	Free air in peritoneum	Excessive examination	Aspiration to release air	Died in 5 hrs.			No P.M.
7	None	None	Expectant			Ceased	Perforation of ulcer in sigmoid; diffuse peritonitis

patient (Case 13). Shock, cyanosis and collapse were noted particularly in three cases. In the others it was not marked enough to occasion comment. Confirmatory evidence of perforation was obtained in six cases by x-ray examination showing free air under one or both leaves of the diaphragm. In three cases the absence of a pneumoperitoneum was specifically noted. Abdominal puncture yielded positive information in three instances.

Precipitating factors. In three cases gastrointestinal x-ray examination seems to have been a direct precipitating factor in the perforation. In two of these cases, perforation, as judged by the symptoms, occurred during the examination; in the other case, it occurred three hours later. Observations of a similar nature appear in the literature. It seems more likely that hyperperistalsis or muscle spasm plays the predominating rôle in the causation than does palpation, although the latter at times may be responsible. It is assumed that the barium itself produces a heightened irritability of the circular and longitudinal muscle fibres resulting in the perforation. Experimentally, barium, introduced aseptically into the peritoneal cavity of dogs (Paas (3)), has resulted in death in twenty hours from a bacterial peritonitis. The barium acts as a foreign body and becomes encapsulated rather than absorbed. The significance of this will be discussed under mortality and prognosis. In two cases gastric lavage precipitated perforation.

Diagnosis and therapy. In spite of the difficulty in the diagnosis of actual perforation, in six cases operation was performed within two hours after the accident. In one case six hours elapsed before operation; in three cases there was an interval of at least twelve hours. In three cases, operation was not carried out at all. In one, the patient was in extremis; in another, the perforation was an unsuspected autopsy finding; and in a third, the perforation was a terminal manifestation.

Prognosis and mortality. Despite the fact that all but one case in this series were recognized clinically, the mortality was comparatively high. Of the ten operated cases, six recovered, four ceased, an operative mortality of 40 per cent. The time interval elapsing between perforation and operation bears the same general relationship to prognosis as in all reported series of perforated lesions of the stomach and duodenum. In this group, with one exception, all cases operated upon within six hours of the perforation recovered. The exception was a patient who perforated following barium meal examination and in whom barium was found freely dispersed in the peritoneal cavity. In spite of prompt surgical intervention (one and one-half hours) the patient succumbed with a general peritoneal infection. In the two other patients who perforated following barium meal examination, one was so shocked that operation was not deemed feasible. In all patients in whom either barium meal examination or gastric lavage preceded perforation death ensued irrespective of the time interval elaps-

ing. The altered prognosis caused by these precipitating factors is no doubt contributed to by the overwhelming peritoneal sepsis incident to lavage fluid inundating the peritoneal cavity and by the toxicity and chemical irritation of barium.

Small intestinal perforations. We have encountered two cases of ileal perforation (Table II). In one, the clinical picture was complicated by an intestinal obstruction caused by gall stones obstructing the ileum, which in turn resulted in a decubital ulceration with perforation. The diagnosis was not made clinically. In the other case, frank evidences of perforation occurred. The patient was operated upon approximately fourteen hours after a perforation caused by a lymphosarcoma of the ileum. Death ensued of a general peritoneal infection.

Large intestinal perforation. Seven cases comprised this group (Table III). In all but one, chronic ulcerative colitis (six non-specific, one amoebic) was the underlying causative factor. The one exception was a young man with a huge megacolon who perforated a stercoral ulcer. Free air was aspirated from the peritoneal cavity. Shock and collapse supervened so promptly as to make operation impossible. There was no post-mortem examination. In contradistinction to the perforations encountered in the stomach or duodenum, perforations of the colon are attended by much more difficulty in diagnosis and this complication in the cases reviewed has been uniformly fatal. There are certain circumstances which contribute to this dismal picture. The patients are chronically and desperately sick. They usually are suffering from an acute exacerbation of a devastating and debilitating illness of long standing. Meteorism, abdominal cramps and tenderness are so intimately a feature of the clinical picture that supervening perforation is difficult to appreciate. Peritoneal reaction is so common in this group of patients because of the deep sub-peritoneal ulcerations that almost inappreciable changes in the abdominal picture ensue following actual perforation. While in a number of cases the complication was suspected, in others exitus occurred with the lesion first demonstrated at post-mortem examination. In contradistinction to the ulcer group, the patients in this group perforated much later after admission. The high mortality is contributed to by the underlying constitutional disease and the resultant fecal peritonitis. Whether chemotherapy will influence this uniformly fatal complication remains to be seen.

SUMMARY

Twenty-two cases of free intra-peritoneal perforations of the gastrointestinal tract occurring during hospital residence are reviewed. Thirteen of these occurred in the stomach and duodenum, two in the ileum, and seven in the colon. Of this number, six recovered after operation. Factors in causation, prognosis, and differences in the clinical groups both as to diagnosis and prognosis are discussed.

CONCLUSIONS

In spite of closer observation and diagnostic competency available in hospital wards, perforations of the gastrointestinal tract occurring under observation have a mortality that seems higher than that in corresponding conditions with which patients are primarily admitted.

Every effort should be made to appreciate minute differences in symptoms and objective findings in patients in whom a potentially perforated lesion is likely to exist.

Promptness in diagnosis and surgical intervention is a deciding factor for a more favorable prognosis.

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OCULAR TENSION AND INTRAOCULAR CIRCULATION

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The ocular tension is to a great extent dependent on the intraocular circulation, although there are several other factors which affect it. The normal ocular tension is equivalent to the pressure of a column of mercury 15 to 20 mm. in height, and is measured as a rule with the Schiøetz tonometer. The latter has supplanted digital palpation, the method formerly in use. Ocular tension represents the balance between secretion and reabsorption of the ocular fluids. Of these the aqueous humour of the anterior and the posterior chamber (the latter between the iris and the lens) ranks first. However, the suprachoroidal fluid (between the choroid and the sclerotic) should not be overlooked. In cases of acute ocular hypertension this may be considerable in amount as for instance in acute glaucoma. If an operator wishes to perform an iridectomy upon an eye in which the anterior chamber is very shallow because the iris is pressed against the cornea, he performs, if he is wise, a "posterior sclerotomy." In this he plunges a cataract knife into the eyeball in a meridional plane at a secure distance back of the ciliary body, and makes a cut of about 5 mm. through the sclerotic. This enables the anterior chamber to become deeper and the iris recedes from the cornea. This in turn facilitates incision with the keratom and prevents enclosure of the "iris angles" into the wound, which would be apt otherwise to nullify the benefit of the operation. In posterior sclerotomy, in cases of acute glaucoma, the first thing to appear is not a bead of vitreous, as one might expect, but a burst of watery fluid, evidently edema fluid transuded from the choroidal vessels into the space between the choroid and the sclerotic.

The aqueous humour is secreted by the ciliary processes into the "posterior chamber", whence it circulates freely through the pupil into the anterior chamber. It is reabsorbed into circulation by the "Pectinate Ligament", consisting of loose connective tissue in the "angle of the anterior chamber" between the root of the iris and the sclerotic. From this it passes into the so-called "Canal of Schlemm", a circular venous sinus in the most anterior part of the sclerotic not far behind its junction with the cornea.

These are the teachings of almost every textbook, but are far from exhausting all the facts. That the aqueous humour is secreted (not transuded) by the ciliary processes is undoubtedly correct. The latter

are frequently alluded to as "glands", but if we come to the question of the reabsorption of the aqueous, we can glean important additional knowledge by examining the manner of action of so-called miotics and mydriatics in ocular hypertension. (Miotics are the drugs which, locally applied, contract the pupil. Mydriatics are the drugs which, locally applied, widen the pupil). Miotics relieve and mydriatics aggravate the hypertension.

Ocular hypertension, apart from changes due to chemical alterations of the blood, depends to a great extent on intraocular circulatory conditions. Miotics and mydriatics exert a powerful influence on this circulation, miotics increasing it and mydriatics retarding it. It will, therefore, be necessary to discuss the mechanism of their effect upon the intraocular circulation. This will be taken up first in an analysis of the relation of the size of the pupil to the circulation of the iris.

The normal width of the pupil depends on two factors: 1) the state of contraction of the sphincter muscle (which is controlled by the amount of light acting upon the center of the retina) and 2) the state of the iris circulation. It will, therefore, be necessary to say a few words on the anatomical structure of the iris and of the choroid.

The Structure of the Iris. Going from front to back we encounter: 1) a thin layer of endothelial cells; 2) the anterior limiting membrane; 3) the "vascular layer", the most voluminous of the iris layers, consisting of loose sponge-like tissue. It contains the iris arteries, which are radially arranged, tortuous, and surrounded by connective tissue with many elastic fibres; it contains also capillaries and veins, also radially arranged and located mostly on the posterior surface. The vascular layer also contains the sphincter muscle itself; 4) the posterior glass membrane, an extremely thin, homogenous elastic membrane, which by certain methods of preparation shows radial striation. It has been taken for a muscle, and called the *dilator* of the pupil (which, in a sense, it is by reason of its elasticity). However, against its muscular nature speaks the fact that in thickness it does not approach the diameter of smooth muscle fibres; 5) the pigment epithelium on the posterior iris surface.

The Structure of the Choroid. Proceeding from inside towards the surface we find: 1) the pigment epithelium, which rightly belongs to the retina; 2) the glass membrane; 3) the choriocapillaris; 4) the vascular layer, the most substantial part of the choroid, containing the larger arteries and the extensive venous system; 5) the suprachoroid, a loose connective tissue between the choroid and the sclerotic, which in cases of acute glaucoma contains a voluminous watery fluid, transuded from the choroidal blood vessels.

Something should also be said about the *anterior ciliary veins*. These collect blood from the ciliary body (muscle) and adjoining parts of the sclerotic. They *perforate the sclerotic* (from within outward), about 5 mm. from the corneoscleral junction, then turn backwards, join other

veins from the episclera, and together with these form larger veins (not visible) which run along or under the external eye muscles to end in the ophthalmic vein. The points of perforation of the sclerotic are visible, and in cases of ocular hypertension look distended. At these very points the anterior ciliary veins receive small tributaries from the ocular conjunctiva and episclera, and these (often erroneously called "anterior ciliary veins") appear engorged in cases of ocular hypertension, so that the experienced physician can by inspection alone, without palpation, conclude that hypertension is present.

Circulatory Effects of the Miotics. Physostigmin (Eserin), pilocarpin, muscarin, locally applied by instillation, have all the same effect but in decreasing strength in the order named. They contract the pupil by stimulating the oculomotor nerve endings in the sphincter muscle and cause a spasm of accommodation. They are also said to paralyze the "dilator", which has been supposed to exist in the form of radial fibres of muscle on the posterior surface of the iris, just beneath the pigment epithelium. In the human eye, as already mentioned, there is no dilator muscle. On this point the best authorities are agreed (the most noteworthy of these being Schwalbe). Dilator action exists, nevertheless, and is represented by elastic fibres surrounding the iris arteries. These fibres are radially arranged and tortuous, following the course of the arteries. They become elongated and straight when either contraction of the sphincter or congestion stretches the arteries. One sees readily that congestion of the iris arteries must straighten them, broadening the iris and contracting the pupil. Congestion of the iris arteries, therefore, opposes and overcomes the dilator effect of the elastic fibres ("paralyzing the dilator"). There is a classical experiment proving this, which the writer has performed many times, when staining the corneal nerves by introducing methylene blue into the circulation. If one injects a solution of methylene blue into the aorta of a freshly killed white rabbit, one can observe in the same instant the iris becomes blue and the pupils contract.

In iritis we find the pupil small because the iris arteries are congested. Every agency which tends to increase the flow of blood to the head makes the pupil small; morphine, chloroform, chloral and similar agents act thus through the circulation. Contrariwise, everything which drains blood from the head dilates the pupils, a fainting spell, death.

Of the miotics, pilocarpin is the most representative and the most important. Eserin acts more powerfully, even too powerfully, and may cause painful cramp-like contraction of the muscle of accommodation. It is apt to cause "posterior adhesions" of the pupil to the lens-capsule, possibly as a result of extravasation of fibrin from the excessively congested iris arteries. Pilocarpin is an alkaloid extracted from "Pernambuco Jaborandi", the leaves and twig tips of a South American plant, "Pilocarpus Pinnatus". Suitable doses brought into the general circulation

by subcutaneous injection increase secretion of the sweat, tear, salivary, gastric and intestinal glands, and produce vomiting. All these effects are stopped by atropine.

Instilled into the conjunctival sac pilocarpin produces miosis and spasm of the muscle of accommodation, which shows itself by apparent myopia of low degree. When used in an eye whose pupil has previously been dilated by atropine or another mydriatic, the miosis is of shorter duration, after which the mydriatic effect asserts itself again.

The contraction of the pupil is due to two factors, stimulation of endings of branches of the oculomotor nerve which pass to the sphincter muscle and dilatation of the iris arteries. Previously the latter effect was supposed to result from paralysis of filaments of the sympathetic nerve which innervate the "dilator iridis". In the human eye, as already stated, no dilator muscle has been proved to exist, but rather a dilating force caused by the radial pull of the peri-arterial elastic fibres in the vascular layer of the iris. This pull tends to keep the arteries tortuous, while the flow of blood tends to straighten them. When in death the iris arteries become empty, the elastic pull of these fibres is unopposed and the pupil becomes very wide. The correctness of this view is proved further by the fact that a pupil dilated by a mydriatic becomes wider still if, in addition, cocaine is instilled. Cocaine has a very strong vasoconstrictor effect, whereas it does not affect the sphincter or the accommodation. If this strong vasoconstrictor effect is added to the weaker vasoconstrictor effect of other mydriatics, the maximal possible widening of the pupil is attained.

It is a very important fact that pilocarpin dilates the iris arteries. There are few authors who have recognized this. Quoting from Schiek and Brueckner's *Handbook of Ophthalmology*, Vol. IV, pg. 781: "Dilatation of blood vessels of the iris was observed by Thiel through examination in redfree light. Koller also points to the vasodilating effect of the miotics. A further support of this view is found in the experimental observations of K. Schmidt, who after injecting pilocarpin into the vitreous of the rabbit's eye, in spite of considerable lowering of tension, found increase of weight of the enucleated eyeball. This is proof, that pilocarpin causes gorging of the blood vessels".

The Normal Tension of the Eye. This, as shown by animal experimentation, is influenced by pilocarpin first by an insignificant increase of 2 to 3 mm. Hg followed after 5 to 10 minutes by a lowering of tension. This has been confirmed by other observers.

The Effect which Miotics have in Reducing Ocular Hypertension. This is explained in textbooks by their pull of the root of the iris away from the cornea at the angle of the anterior chamber, thereby, "freeing the angle of the chamber" and enabling the "Pectinate Ligament" to exert its function of reabsorbing the aqueous humour. All this is supposed to be accom-

plished by the contraction of the sphincter. In reality there is much more than this. As the author and others have shown, miotics dilate or congest the iris arteries which, by their stretching effect, increase the contracting effect of the sphincter upon the pupil. When the circulation of the blood in the iris is speeded up, the absorption of the aqueous humour and other ocular fluids is likewise facilitated. This explains also the beneficial effect of hot applications to the eye or side of the face in reducing ocular hypertension. This also explains the beneficial effect of morphine, acting through the general circulation and the favorable effect of dionine, which causes a powerful and stormy local congestion and incidentally also contracts the pupil (which is not generally known), although in a weak and indecisive way. The contracting effect of dionine on the pupil is probably not due to any direct action upon the sphincter but to congestion and stretching of the tortuous iris arteries.

Contrariwise the bad effect which *mydriatics* have on ocular hypertension and their power occasionally to precipitate an attack of glaucoma in predisposed individuals is explained in the textbooks by a mechanical "blocking of the iris angle" which prevents the "Pectinate Ligament" from functioning properly. There are probably additional causes for this influence. Mydriatics also constrict the iris arteries. This vasoconstricting effect adds to the sphincter-paralyzing effect in producing dilatation of the pupil. This is shown convincingly by instilling cocaine into an eye whose pupil has previously been widened by a mydriatic. Cocaine has the strongest vasoconstricting effect of all mydriatics, yet has hardly any effect on the sphincter. Nevertheless, it causes in fact the maximal mydriasis possible to obtain. In mydriasis the circulation in the iris is reduced, the ciliary processes are in turn congested, the large veins of the choroid are engorged, and the reabsorption of ocular fluids is hampered. At the same time one witnesses the gorged aspect of the "anterior ciliary veins" (or rather, as explained before, the affluent conjunctival and episcleral tributaries, which join the real anterior ciliary veins, stopping short at the point of dilatation where the latter perforate the sclerotic).

In cases of hypertension of acute and subacute glaucoma we find the pupil irregularly dilated (oval), not because of any paralysis of the sphincter, but as an expression of anemia of the iris arteries in some of the sectors. In contrast to this arterial anemia, the venous system of the choroid is engorged, of which condition the aspect of the bulbo-conjunctival branches of the anterior ciliary veins gives emphatic evidence. This contrast of the circulation, arterial anemia, and venous engorgement is characteristic of acute glaucomatous hypertension. The spasm of the arteries sets up an obstacle to the flow of blood through the capillaries and veins, the "*vis a tergo*" being insufficient, so that the blood stagnates. The beneficial effect of miotics is explained, therefore, by their speeding

up of the ocular circulation, and the harmful effect of mydriatics, of which cocaine is an outstanding example, by vasoconstriction. Cocaine alone, or combined with a weak mydriatic like Euphthalmin, is capable of precipitating an acute attack of ocular hypertension in a predisposed individual. The writer knows of his own experience, among other cases, that of a famous French ophthalmologist who in the first days of cocaine, over 56 years ago, unwittingly released an attack of glaucoma by instilling cocaine into his own eye.

A CONGENITAL CARDIAC ANOMALY: ATRESIA OF MITRAL ORIFICE AND SEPARATION OF LEFT AURICLE AND VENTRICLE

WITH AN APPENDED CASE OF ABSENT LEFT VENTRICLE

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True atresia of an auriculo-ventricular orifice is a very rare form of cardiac anomaly, and especially so on the left side of the heart. In the case reported below, in addition to several other developmental defects, not only was there no orifice between the left auricle and ventricle, but also the two chambers did not appear to have any connection and were actually separated by a space of 5 mm. at their nearest points.

CASE REPORT

History. A black female was born May 17, 1940, of apparently healthy parents. The mother had had two previous healthy children. Pregnancy lasted 32 weeks; labor, 18 hours. The fetal heart sounds had been heard 10 days before delivery. The body weighed 1570 gms., and measured 34 cm. in length. After delivery, the heart was observed to have given several beats, but the baby did not breathe or move.

Autopsy ('40—639—Dr. Harold M. Horack; 24 hours after death). In addition to the cardiac anomalies, to be described below, there were found: spina bifida with meningocele of the cervical cord; absence of left radius, left adrenal and left kidney. The lungs were completely atelectatic; they had the usual number of lobes.

The *heart* weighed 7 gms. The bulk of the heart is made up of a dilated and hypertrophied right ventricle measuring externally 2.6 cm. in length by 1.8 cm. at greatest transverse diameter. From this a relatively large arterial trunk (pulmonary ?, transposed aorta ?) arises. Adjacent to, and communicating with, this chamber by means of a small interventricular septal defect, is an extremely small and rudimentary left ventricle, which measures about 8 mm. in length by 3 mm. in diameter. The capacity of this chamber is about 0.1 cubic centimeter. Arising from this rudimentary ventricle there is a small, thin-walled arterial trunk (8 mm. in circumference) which has, at its origin, a valve with two minute, thickened, and imperfectly formed cusps. (The arterial wall appears somewhat wrinkled after fixation.) The orifice between the cusps is small, and the valve appears stenotic. The interventricular septal defect (2 mm. in diameter) extends from the base of the rudimentary ventricle to a point just below the origin of the major arterial trunk in the large ventricle. The major arterial trunk (pulmonary artery ?) is supplied with a valve measuring 16 mm. in diameter. Its three cusps are normal, except for being slightly unequal in size. The coronary arteries have their origin in the sinuses behind the two smaller cusps; the left coronary arising from the anterior sinus and the right coronary from the posterior sinus.

The heart has two auricles: the right is hypertrophied and dilated, its cavity measuring approximately 1 cm. in length by 0.8 cm. in diameter; the other is small and hypoplastic (approximately 0.6 x 0.5 cm.). The larger auricle is about 3 to 4

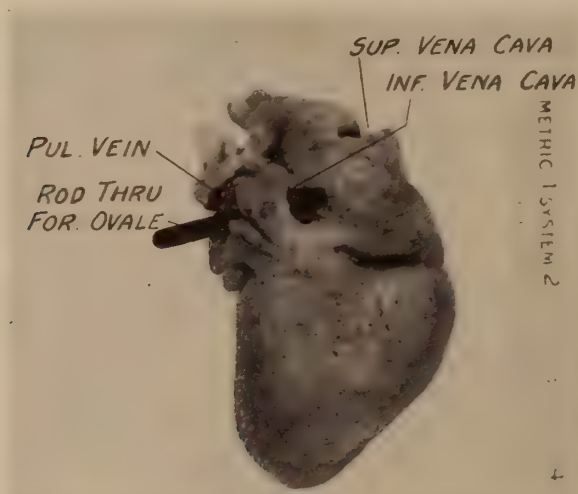


FIG. 1. Heart—Posterior view. A large rod extends from the left auricle through the foramen ovale into the right auricle, where it is seen through the opening of the posteriorly placed inferior vena cava. The stumps of one of the pulmonary veins and the superior vena cava can be seen. The greater size of the right auricle is obvious; no part of the diminutive left ventricle is visible.



FIG. 2. Anterior aspect of the opened heart. Above the small left ventricle (L. V.) is the opened, slightly wrinkled aorta (Ao). The label R. A. sits on part of the tricuspid valve. The left auricle lies behind the opened pulmonary artery.

times the size of the smaller. The two auricles communicate through a widely patent foramen ovale 3 mm. in diameter. Part of the adjacent septum is membranous. Between the large right auricle and ventricle is a functioning valve (23 mm.

in circumference) that is supplied with two large and one small, thin, freely movable leaflets. These are not completely separated from each other and might be regarded as two leaflets. No point of communication between the small auricle and the rudimentary ventricle could be identified; in fact, the lumina of the two chambers at their nearest points are at least 5 mm. apart. The great veins were not examined *in situ*, but insofar as can be determined now there is no gross abnormality other than the greater size of the vessels returning to the right auricle. These are much larger and sturdier than the pulmonary veins. The inferior vena cava enters the auricle much more posterior and nearer the septum than is normally the case. There is a relatively large and patent ductus arteriosus which communicates between the major and minor arterial trunks mentioned above. (This was not included in the preserved specimen.)

Microscopic Examination. A section was taken horizontally (heart upright) extending from the wall of the diminutive left ventricle, through the interventricu-

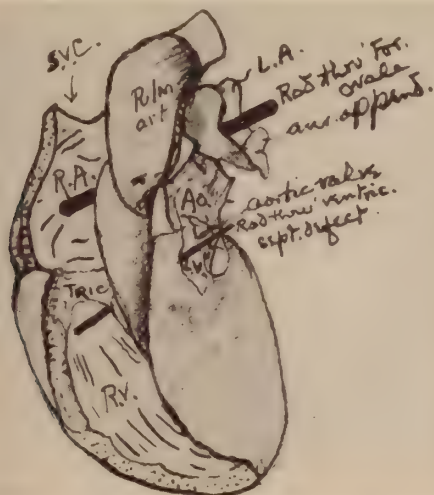


FIG. 3. Semi-diagrammatic drawing of the same aspect as Fig. 2, showing the considerable space between left auricle and left ventricle, with rods through the septal defects.

lar septum, the base of the right ventricle (intervening between left ventricle and auricle) and the left auricle. It showed a myocardium normal for a full-term infant. No differences could be detected in the muscle fibers of the two ventricles. No abnormal collections of cells or connective tissue were seen, to suggest present or past inflammation. Sections from the walls of the two arteries likewise showed no abnormalities, so that the wrinkling noted above is taken to be a fixation artefact.

Probable Explanation of the Cardiac Anomaly. The primary defect here seems to have been the closure of the communication between the left auricle and ventricle. Presumably, the heart had been divided in the second month of fetal life into its four chambers by the auricular and ventricular septa and the endocardial cushions of the auriculo-ventricular canal. As the defect is presumably one of development (no signs of fetal heart disease, and also the presence of other anomalies), one may assume an overdevelopment of the endocardial cushions on the left side until they met and obliterated the auriculo-ventricular orifice, after the interventricular septum had been almost completely formed. In this event, very little blood reached the left ventricle, so that it and its artery remained markedly hypoplastic.

Similarly the flow of blood out of the left auricle was inhibited and it too remained hypoplastic—the right heart practically performing the work of both sides, the extracardiac distribution of blood being mainly accomplished through an unusually large ductus arteriosus. With the continuing hypertrophy of the right heart and the left remaining stationary in size and the left auricle relatively fixed, the diminutive left ventricle was gradually pulled by the growth of the right ventricle further and further from the auricle with which it had originally been connected.

The presence of a cardiac anomaly was not suspected until after the heart was removed from the body, and unfortunately the autopsy record did not contain detailed statements about the arterial distribution (location of origin of innominate, subclavian, carotid arteries, course of systemic aorta). It is not possible, therefore, to say definitely whether the large artery coming from the right ventricle was the pulmonary artery or a transposed aorta. The origin of the coronary arteries from

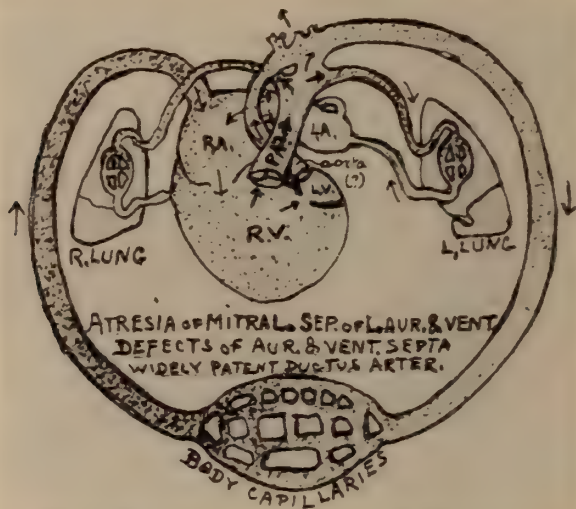


FIG. 4. Diagram (after Maude Abbott (1)) to show the probable course of the blood, if the infant had survived. Arrows indicate the course of the blood stream, and the stippling indicates the proportion of oxygenation. The unstippled left auricle (oxygenated) would probably have contained some venous blood.

this vessel would point more definitely toward its being the aorta if it were not for the fact that coronary arteries have been observed arising from the pulmonary artery (5). In either case, the dynamics of the circulation would be essentially the same, the arterial blood going to the systemic aorta and its branches directly in the latter case (transposed aorta) or from the pulmonary artery through the wide ductus arteriosus in the former case. The blood returning from the lungs through apparently normal pulmonary veins had the widely patent foramen ovale as the only means of exit. Presumably, however, the hypertrophied right auricle pumped some blood through the foramen into the left auricle with each auricular systole, so that there was an ebb and flow between the auricles, such as might be pictured between an auricle and its auricular appendage.

The disturbances in blood flow produced by the primary anomaly prevented the closure of the interventricular septum, and kept the foramen ovale more widely open. That considerable blood passed through the ventricular septal defect is

shown by the fact that the aorta (?) is considerably larger than would be required by the diminutive left ventricle. (The slightly thickened cusps are the only items at all suggestive of fetal inflammatory disease; but they seem better explained as minor developmental variations.) It is worth noting that all the unilateral anomalies were on the left side.

COMMENT

A careful, but by no means exhaustive, search of the literature has failed to reveal another case where the auricle and ventricle were actually separated from each other, as well as having their connecting orifice closed. Incidentally this search was unnecessarily complicated, even in Maude Abbott's (1) well known Atlas, by the misuse of the term "atresia" (congenital absence or pathological closure of a normal opening or passage, lit., without a hole) where "stenosis," or narrowing, was meant.

True atresia of an auriculo-ventricular valve is a rare anomaly. Poynter (7) cites a number of cases of single atrio-ventricular opening, but these include many *corda bilocularia* or *trilocularia*, and of the remainder most are in the right heart. Two of these throw some light on possible ways of development of the atresia. In the Rogers and Fortiscue-Brickdale (9) case the right ventricle was "separated completely from the dilated right auricle by a smooth membranous septum into which the *chordae tendineae* were inserted." Kühne (6), on the other hand, in a case of tricuspid atresia found a "thick muscle plate" separating the right auricle and ventricle. In a third variety, Schreiber (10) found in a cyanotic child of 2½ years the tricuspid orifice replaced by scar tissue. As there were also vegetations present on the mitral valve, and an obliterative pericarditis, it is reasonable to conclude that the atresia was here the result of inflammatory disease. Thus it appears that atresia of an auriculo-ventricular orifice may be due to at least three possible mechanisms: 1) early closure by overgrowth of muscle; 2) fusion of valve leaflets after formation of papillary muscles and chordae (developmental ?); 3) intrauterine inflammatory disease.

Atresia of the left auriculo-ventricular orifice is much rarer than atresia of the orifice of the right side. In Vernon's (11) second case, which lived eight days, the left auricle was "very small, in fact, a mere diverticulum from the right auricle; it received two pulmonary veins, one from each lung, and communicated with no other cavity than the right auricle. The ventricular portion of the heart was single and did not present the slightest vestige of a septum."

The heart that comes closest to the one here reported is that shown in Figure 4 of Sir Arthur Keith's (4) article. It was from an otherwise healthy child who became cyanotic sixteen hours after birth, and died after forty-eight hours. The left auriculo-ventricular orifice was obliterated, and the left ventricle diminutive, only a trace of these structures being visible. The proximal aorta was stenotic, attaining normal size distal to the widely

dilated ductus arteriosus. The left auricle was small, its blood reaching the right heart by way of the foramen ovale. It appears to have been in contact with the left ventricle, though their chambers did not communicate.

Reefschläger (8) reports the case of a cyanotic child who died at the age of one year and eight months. Autopsy revealed a *situs inversus totalis*, and a trilocular heart with the single ventricle connected with the right auricle and both arteries, but not with the left auricle (which, of course, received venous blood). He refers, also, to cases of obliteration of the auriculo-ventricular orifice, observed by J. Steiner (*Traité des maladies de l'enfance*) and by Grancher (*Dict. Encyclopédique*). Grothe (2) also observed a case of *situs inversus* in a child of five weeks, where the atrophic left (venous) ventricle was connected with the right auricle but not at all with the left (venous) auricle. In Jacoby's (3) so-called *cor biloculare* of a 14-day-old child, the cord-like pulmonary artery ended in a blind sac (rudimentary right ventricle?) at the base of the heart. This serves as an illustration of the principle that if the rudimentary chamber has no communication with another chamber, the non-functioning artery shrinks to a cord-like structure, but if a septal defect persists, as in the case here reported, the artery continues to function with less reduction in size.

Most of the reported cases of auriculo-ventricular atresia have lived several hours, days or even months; some were even reported as not cyanotic for varying periods after birth. It is hard to understand how cyanosis was avoidable. It is also hard to understand why this particular cardiac anomaly apparently has not been previously observed.

SUMMARY

A heart of a still-born infant is reported, in which the left auriculo-ventricular orifice was obliterated, and the left auricle separated from the left ventricle by a distance of several millimeters. From the diminutive left ventricle, which was connected with the large right ventricle by a small septal defect, a small aorta (?) emerged that communicated with the large pulmonary artery (?) by a widely patent ductus arteriosus. The foramen ovale was widely open. The coronary arteries arose from the large artery. Other congenital anomalies were present, the unilateral ones all being on the left side. The heart beat was heard before and after delivery, but the child did not breathe or move.

AN APPENDED CASE OF ABSENT LEFT VENTRICLE

Dr. W. F. Sheldon has recently performed an autopsy (University of Pennsylvania Hospital, P.M. 41-1249) on a 48 hour old negress, where there was complete absence of the left ventricle. The small left auricle passed the blood from the lungs through the foramen ovale to a large right auricle thence to a large right ventricle. The mitral area was replaced by dense connective tissue. The large pulmonary artery com-

municated through the patent ductus arteriosus with a hypoplastic aorta, that had its normal tributaries (including coronaries). The aorta could be traced proximally to a blind pouch at the base of the right ventricle, the probe point being palpable from the right ventricle through the septal leaflet of the normal tricuspid valve. No vestiges of aortic or mitral valves were found. It is not yet clear whether the aorta was connected with an undetected extremely hypoplastic left ventricle (as in the case reported above), or whether the large ventricle represents a common chamber with complete failure of the ventricular septum to develop, yet with division of the truncus arteriosus and closure of the proximal end of the aorta. The infant was born at full term, two other children being healthy; no history of syphilis. It first became cyanosed shortly before death. No other congenital anomalies were noted.

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PRESSOR KIDNEY EXTRACTS ("RENIN") AND THE PRODUCTION OF CARDIAC AND GASTRO-INTESTINAL HEMORRHAGES AND NECROSES IN DOGS WITH ABNORMAL RENAL CIRCULATION

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During the course of a large series of experiments dealing with the response of dogs with abnormal renal circulation to various pressor kidney extracts, administered intravenously (1, 2) a number of animals at death exhibited striking hemorrhagic and necrotic lesions, most abundant in the gastro-intestinal tract and the heart. Similar lesions have been described under different experimental conditions (3, 4, 5, 6, 7, 9) and generally accepted as the analogue of the pathological changes found in the malignant phase of human hypertension. The following brief protocols describe the facts of the experiments.

PROTOCOLS

Dog 90, with a control mean femoral blood pressure of 120 mm. Hg, had the *left renal artery partially clamped* (Goldblatt technic) on January 9, 1939. The blood pressure rose to 160 to 180 mm. Hg. On January 25 dilute pig KE¹ was injected for almost 5 hours, without ill effects. *Right nephrectomy* was carried out on February 5 and dilute pig KE¹ again injected for 101 minutes on February 7, when the control blood pressure was 156 mm. Hg. The blood non-protein nitrogen was 56 mg. per cent on February 8, and 86 mg. on February 20, two days after *further clamping of the left renal artery*. On February 23, when the blood pressure was 200 and the blood non-protein nitrogen 58 mg., dilute pig KE was injected for 88 minutes. The dog had convulsions the next day and was killed. *Autopsy* showed a small, partly necrotic left kidney with a few hemorrhages; numerous linear hemorrhages over the lower ileum; hemorrhagic necrosis of most of the right ventricular wall, less in the left ventricle, septum and auricles; a small hemorrhage into the right vitreous. The microscopic changes are illustrated in figures 1A and B.

Dog 71, with a control mean femoral blood pressure of 124 to 140 mm. Hg, was injected with dog KE in varying amounts on 9 occasions between

*The authors are indebted to Dr. David Klein, Wilson & Co. Laboratories, Chicago, for the hog kidney used in these experiments.

¹ KE denotes pressor kidney extract or "renin."

March 23 and September 20, 1938 without ill effects. The *left renal artery* was partially clamped on March 15, 1939. Pig KE, 10 cc., was given on March 21 when the mean blood pressure was 168. The *right renal artery* was clamped on March 28; the blood non-protein nitrogen was 111 mg. per cent on March 29. Pig KE, 13 cc., was given on March 30, raising the blood pressure from 176 mm. to 300 mm. Hg temporarily. A rapid return to the control level suggested anaphylaxis. The blood non-protein nitrogen was 204 mg. the next day; the dog was frankly uremic and was killed. *Autopsy* showed 75 cc. of thin blood fluid in each pleural cavity; many subendocardial hemorrhages in the right ventricle and a few in the left

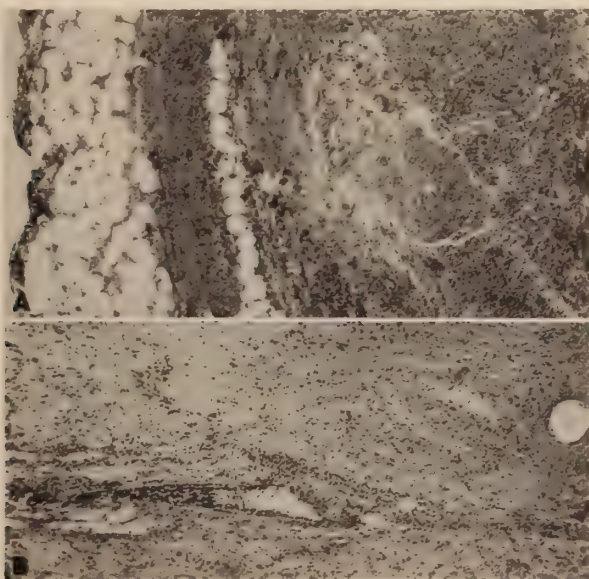


FIG. 1A. Dog 90. Section through most of auricular wall showing epicardial, sub-epicardial, and myocardial hemorrhages, necrosis of muscle, degeneration of arterioles, and some leucocytic infiltration. $\times 90$.

B. Dog 90. Section through left ventricle showing extensive interstitial hemorrhage, necrosis and hemorrhagic dissection of wall of arteriole and leucocytic reaction in and about wall of venule. $\times 100$.

ventricle and auricles; a necrotic left kidney with hemorrhagic pyramids and a fatty right kidney. The diaphragm was also streaked with hemorrhagic necroses. The microscopic picture is demonstrated in figure 2.

Dog 88, with a control blood pressure of 102 to 122 mm. Hg, had the left ureter ligated October 8, 1938, received dog KE 6 times in varying dosage between October 29 and November 17, and pig KE 4 times between December 13, 1938 and March 2, 1939. On March 6, intravenous pyelography showed a large hydronephrotic sac on the left. The blood non-protein nitrogen was 24 mg. per cent on March 9. The *right ureter* was partially

clamped on March 11 and pig KE, 12 cc., was injected on March 14 when the blood pressure was 146 mm. Hg. There was no anaphylaxis. On March 15, the blood non-protein nitrogen was 65 mg. and on March 20 the dog was vomiting and weak, evidently uremic. *Autopsy* showed a narrow subcapsular hemorrhage over the moderately hydronephrotic right kidney and a huge left renal sac; many hemorrhages in the left ventricle and auricle, fewer on the right side but extending into the root of the pulmonary artery; no gross gastro-intestinal nor diaphragmatic lesions.

Dog 107 had the left ureter constricted on August 28, 1939, and the right renal artery partially clamped on September 27. The blood non-protein nitrogen was 33 mg. per cent on October 4. Pig KE was injected on October 12 when the mean blood pressure was 200 mm. Hg, also on October 13, when the dog had clinical uremia. The blood non-protein nitrogen



FIG. 2. Dog 71. Section through area of subendocardial hemorrhage and necrosis in right ventricle, showing fibrinoid arterioles and considerable leucocytic infiltration. $\times 215$.

was 114 mg. on October 14 and 208 mg. on October 16, the day of death. *Autopsy* showed innumerable hemorrhagic lesions in the gastro-intestinal tract, the diaphragm, and in all chambers of the heart; moderate left hydronephrosis with a few hemorrhages, and a small anemic infarct in the right kidney. The microscopic changes are shown in figure 3.

Dog 120 had the right renal artery partially clamped on May 12, 1940. On May 20, the mean blood pressure was 170 mm. Hg; the left renal artery was constricted. Pig KE was injected for 50 minutes on May 28, raising the blood pressure from 164 mm. to 300 mm. Hg temporarily. The dog died that night. *Autopsy* showed bloody fluid in the pleural and peritoneal cavities; many hemorrhages in the gastro-intestinal tract and diaphragm, some in the heart and pancreas and a few in the right kidney. The microscopic picture is illustrated in figure 4.

Dog 134 had the *left renal artery* partially clamped on January 6, 1941 and the *right renal artery* on January 16. The blood non-protein nitrogen was 198 mg. per cent on January 22. The next day, pig KE, 9 cc., was injected, the control blood pressure being 158 mm. Hg. The dog had many convulsions and died that night. *Autopsy* showed hemorrhagic necrosis of both kidneys; numerous hemorrhages in the lower ileum, colon and sub-endocardially in the left ventricle; about 500 cc. of bloody peritoneal fluid. The microscopic picture is exemplified in figure 5.

Dog 138 had the *right renal artery* partially clamped on January 27, 1941, and the *left renal artery* on February 17. On February 20, the mean blood pressure was 168 mm. Hg and the blood non-protein nitrogen was 25 mg. per cent. Pig KE, 13 cc. was injected. The dog died during the night.

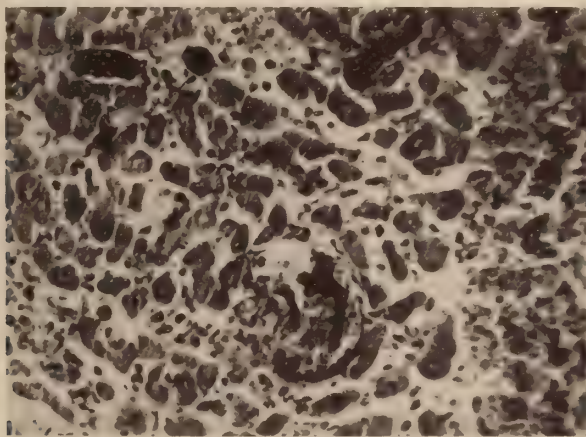


FIG. 3. Dog 107. Section through right ventricle showing numerous necrotic and partly thrombosed arterioles, slight degenerative changes in myocardium and hemorrhage. $\times 425$.

Autopsy showed numerous gastro-intestinal hemorrhages; normal kidneys; many subendocardial and deeper hemorrhagic lesions in the right ventricle and in the papillary muscles of the left ventricle; blood tinged fluid in the body cavities. The microscopic appearance was in all respects similar to those previously illustrated.

Dog 121 had the *left renal artery* constricted on June 7, 1940 and the *right renal artery* on June 24. On July 1, pig KE was injected for 60 minutes, the control blood pressure being 200 mm. Hg. On July 18 and 25, pig KE was again given. The dog was not used again until January 3, 1941 when 2300 cc. of normal saline was injected under nembutal anesthesia. The mean blood pressure was 210 mm. Hg. The dog was killed at the end



FIG. 4. Dog 120. Section through papillary muscle of right ventricle showing fibrinoid degeneration of arterioles and surrounding connective tissue, many foci of hemorrhage and muscle necrosis. $\times 110$.

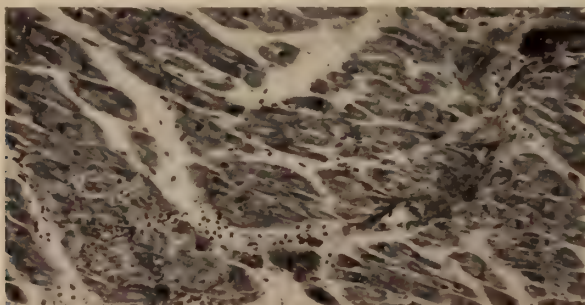


FIG. 5. Dog 134. Section through left ventricle showing early fibrinoid degeneration of arterioles and capillaries and small area of hemorrhage and focal necrosis. $\times 240$.

of the experiment. *Autopsy* showed a few dark spots in the right auricle, mistaken for hemorrhages. The left kidney was somewhat atrophic. The microscopic nature of the auricular lesions is shown in figure 6.

COMMENT

In addition to the animals described in the preceding protocols, there were 6 dogs with similar hemorrhagic lesions, chiefly in the heart and gastro-intestinal tract. In *Dogs 83*, (fig. 7A) 95 and 130, the constriction of both renal arteries was severe enough to produce necrosis of one or both kidneys, severe hypertension and uremia. The possible rôle of pressor kidney extract, injected into these animals, in the production of hemorrhages and necrosis, could not be evaluated in view of the strong probability of the spontaneous development of the lesions under these experimental conditions (7). In *Dog 110*, with a moderate left hydronephrosis, uremia developed 5 days after constricting the right renal artery. There were numerous convulsions on the day of exitus, but the blood pressure was not

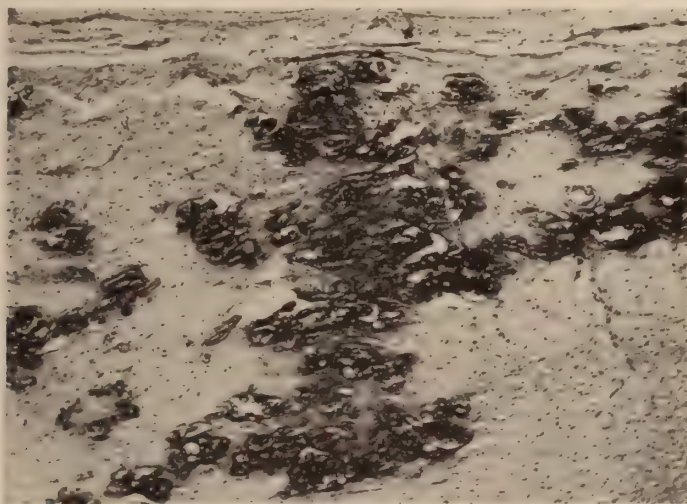


FIG. 6. Dog 121. Section through right auricle showing area of dense fibrosis and calcification, presumably a healed lesion resulting from hemorrhagic necrosis.

taken in the last few days. Presumably, this dog also died in the malignant phase of hypertension. *Dog H5*, with bilateral constriction of the renal arteries, had severe hypertension and uremia without gross renal necrosis. There were numerous hemorrhages only in the heart. Finally, *Dog 119*, with both renal arteries constricted, a mean blood pressure of 178 mm. Hg and no clinical signs of uremia (the blood non-protein nitrogen was not estimated) was very weak after a large injection of a somewhat impure pig kidney extract. The animal was killed on the following day and showed some hemorrhages in the heart (fig. 7B). In this case, the kidney extract seemed to be the most probable factor in the production of the lesions.

A detailed discussion of the gross and histological changes is hardly

necessary in view of the excellent descriptions already published (3, 4, 5, 7, 9). Suffice it to emphasize that in the present observations special attention was directed to the involvement of the heart. Hemorrhages and necroses favored the subendocardium and the subepicardium but often affected the deeper muscle bundles. The right ventricle, the auricles and the papillary muscles of the left ventricle showed the most widespread lesions. Histologically, all degrees of change were observed from small areas of capillary hemorrhage without necrosis of arterioles or muscle fibers to complete hyaline or fibrinoid necrosis of capillaries, arterioles and small arteries, rarely of venules, degeneration and necrosis of myofibers,

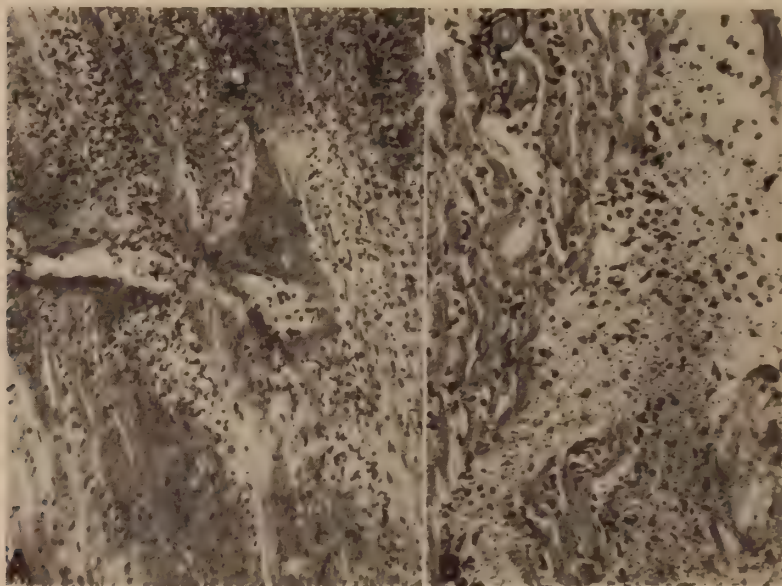


FIG. 7A. Dog 83. Section through left ventricle showing arteriolar necrosis, extensive hemorrhage and muscle degeneration and leucocytic reaction. $\times 175$.

FIG. 7B. Dog 119. Section through right ventricle showing subendocardial hemorrhage, hyaline degeneration of arterioles and muscle fibers, and leucocytic infiltration. $\times 240$.

extensive interstitial hemorrhage, partial thrombosis of arterioles, leucocytic reaction in and about the necrotic areas of myocardium and as perivascular exudate. The extravasated blood was little altered except for some hemolysis. Pigment-containing macrophages were not observed. Since none of the dogs survived the presumptive onset of the lesions for more than a few days, the lack of signs of organization of the injured regions was not surprising. However, in *Dog 121* which was killed some five months after the last injection of pig kidney extract, partially calcified fibrous scars were found in the right auricle (fig. 6). Their appearance strongly suggests healed areas of necrosis.

The pathogenesis of the hemorrhagic and necrotic lesions is an interest-

ing but difficult problem. In the present experiments it is significant that this type of pathology was never observed in dogs with constricted arteries or ureters, or with one or two nephrectomies, which were injected with various preparations of dog pressor kidney extract, at times in large doses. It is possible that those animals which died, or were killed, within a few hours after the injection of extract did not have time to develop lesions. However, this criticism could not apply in general. The absence of lesions in the dogs receiving dog kidney extract is particularly remarkable in view of the widespread changes produced in nephrectomized dogs by the injection of canine renal extracts (7). Possibly, the presence of functioning kidneys may have an important bearing on the development of hemorrhagic necrosis.

On the other hand, the injection of heterologous pig kidney extract was the constant factor in the dogs with hemorrhagic lesions. This was true regardless of the state of purity (absence of depressor effect) of the extract. In fact, in Dogs 79 and 105 which developed hematuria and died after receiving a large amount of a relatively impure pig kidney extract after tolerating many previous injections of other extracts even when they resulted in anaphylaxis, there were no significant hemorrhagic lesions. There had also been no renal insufficiency in either dog at the time of the final experiment.

When the lesions were first observed in Dogs 90 and 71, the suspicion of anaphylactic pathology was aroused because these animals had tolerated homologous kidney extract very well. However, further experience soon showed that anaphylactic reactions were of themselves not significant in the production of the specific lesions. Another striking fact was the uniform absence of fatal reactions, and presumably of significant cardiac or gastro-intestinal hemorrhages, in normal dogs injected with large amounts of pig kidney extract. This was also true of dogs with unilateral constriction of the renal artery or unilateral hydronephrosis and good renal function. All the evidence, therefore, pointed to a necessary combination of serious or bilateral abnormality of the renal circulation and the injection of a sufficient amount of a potent heterologous kidney pressor extract. Under these conditions neither severe hypertension nor uremia is indispensable for the production of hemorrhages and necroses, but their joint presence strongly favors the development of the lesions. Whether the kidney extract acts through its intense vasoconstriction of the arterioles during the period of hypertension or whether it leads to local hyperemia and hemorrhage through a depressor, vasodilator substance (7) cannot be decided. The extracts used in these experiments were uniformly free from obvious depressor activity but may still have contained enough of the agent to give rise to local circulatory disturbances. The reason for the predominance of the hemorrhages in the heart and gastro-intestinal tract is unknown.

The relation of the lesions to the pathology of the malignant phase of

human hypertension is a fascinating problem. Disregarding the striking differences in distribution and intensity of the lesions in the dog and man (on the assumption that species differences are involved) one is tempted to conclude from the available evidence that intravenous injection of extracts of the kidney, whether made *in vitro* by simple or complicated procedures or *in vivo* by small amounts of blood perfusing an ischemic or necrotic kidney, may furnish the *coup de grâce* to animals or men with renal hypertensive disease. Lesser degrees of injury might be tolerated by the subject but eventually result in the "vicious circle of chronic Bright's disease" (10). Such a conclusion would associate experimental and human renal hypertension even more closely than ever before and attribute to renal extracts pathologic import apart from their pressor or depressor activity. But this is not all that the conclusion implies! It also involves the assumption that somehow a normal kidney, or one not too seriously impaired in its circulatory dynamics, can prevent or neutralize the material in kidney extracts responsible for the severe tissue changes. Another possibility is that the state of uremia markedly "sensitizes" the animal to the injurious effects of kidney extracts on tissues and vessels. It should be noted, however, that normal dogs react to crude kidney extracts much as do nephrectomized dogs (8). Finally, the difference in response of the dog with abnormal kidneys to homologous and heterologous kidney extracts requires an explanation. The identical effect of dog and pig kidney extracts injected into nephrectomized dogs is no necessary contradiction in view of the absence of kidney function in these experiments.

SUMMARY AND CONCLUSIONS

The intravenous injection of adequate amounts of reasonably purified pig kidney extract into dogs with constricted renal arteries, constricted artery and ureter, or other types of experimental abnormalities of renal circulation or function, accelerates the development of hemorrhagic necrosis in the heart, gastro-intestinal tract, and elsewhere in the body. Previously described as part of the picture of experimental malignant hypertension (3, 4, 6, 9) on the one hand, and as the result of absorption from necrotic kidney tissue or of the intravenous injection of crude kidney extracts on the other hand (7, 8), the lesions are strikingly similar in the various studies if allowance is made for species differences as well as for marked variation in the experimental conditions.

In the present investigation, neither severe hypertension nor uremia was necessary for the development of the lesions, although most of the dogs with widespread pathology were both hypertensive and uremic.

In contrast to another report (8) the specific lesions were not observed in normal dogs injected with either dog or pig kidney extract, nor in dogs with abnormal kidneys injected with dog kidney extract. Undoubtedly, differences in the methods of preparation of renal extracts are very im-

portant. The possibility that the normal kidney may, in some fashion, prevent the vascular and tissue injury produced by kidney extracts in dogs without kidneys or with abnormal renal circulation, deserves further investigation.

Anaphylactic reactions to heterologous kidney extracts are not responsible for the occurrence of the lesions.

Satisfactory conditions for the regular localization of typical lesions in the kidney of the dog have not yet been devised. Until this has been accomplished, it may be unwarranted to conclude that the experimental pathology is a true analogue of the pathology of malignant hypertensive disease in man. However, the accumulation of evidence in favor of this conclusion is impressive.

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THE ASSOCIATION OF ANGINA PECTORIS OR CORONARY THROMBOSIS WITH MITRAL STENOSIS

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It is well known that aortic valvular disease is not infrequently associated with angina pectoris. It has also been believed that a causal relationship existed between this valvular lesion and the anginal state. In aortic insufficiency, it has been thought that the low diastolic pressure is mainly responsible for the attacks of angina because the early teachings indicated that coronary flow occurred exclusively during diastole, and that with the low diastolic pressure there was insufficient coronary circulation. This explanation is not altogether satisfactory for several reasons. In the first place, angina pectoris is extremely rare in cases of syphilitic aortic insufficiency unless the coronary orifices are narrowed by the syphilitic aortitis. Furthermore, angina pectoris is quite common in aortic stenosis, rheumatic or sclerotic, whether there is an accompanying aortic insufficiency or not. In a previous study (1) the incidence was found to be about 22 per cent. In fact these two conditions may coexist without any significant coronary artery disease. The relationship, therefore, between aortic valvular disease and the anginal state is not simple and must depend on various factors.

Mitral stenosis on the other hand is infrequently associated with the anginal state. In an earlier study (2) it was estimated that about 1 per cent of cases with angina will be found to have mitral stenosis. A more extensive analysis now shows that amongst 2,832 cases of definite angina pectoris or coronary thrombosis seen in private consultation practice in twenty-one years, there were only 17 with mitral stenosis, i.e. 0.6 per cent. The purpose of this review is to reconsider this relationship and to ascertain whether there are any clinical peculiarities in this group of patients and whether the valvular deformity has any bearing on the anginal state.

The material used in this paper was obtained from a study of the clinical and pathological data in the records of the Peter Bent Brigham Hospital from the year 1913 to 1940 inclusive, together with the cases seen by one of us in private consultation practice (Table 1). Only those cases were included which could be regarded as having definite coronary occlusion or classical angina pectoris in addition to undoubted mitral stenosis. All borderline cases were eliminated, as were those having aortic valvular involvement in addition to mitral stenosis. All cases with syphilis or

TABLE 1

	SEX	AGE*	ONSET OF A.P.	DURATION OF A.P.	B.P.	RHYTHM	WT. OF HEART	OCCURRENCE OF COR. OCCLUSION
Necropsy cases								
1	F	55	53	2	140/90	A.F.	560	
2	M	63	57	6	168/85	A.F.	460	
3	F	66	64	2	170/90	A.F.	500	
4	F	65	62	3	142/76	A.F.	390	
5	M	50	49	1	180/110	A.F.	560	Cor. occ.
6	M	52	50	2	150/96	Sinus	900	
7	F	50	49	1	200/95	A.F.	480	
8	F	67	52	15	250/100	A.F.	540	
9	F	69	?	?	120/80	Sinus	420	Cor. occ.
10	F	57	47	10	210/100	A.F.	520	
11	F	69	68	1	210/110	A.F.	560	Cor. occ.
12	M	63	62	1	105/70	Sinus	460	Cor. occ.
13	F	66	65	1	120/80	Sinus	650	
14	M	54	53	1	140/70	A.F.	740	
15	M	66	56	10	142/94	Sinus	430	
16	F	50	49	1	190/110	A.F.	500	Cor. occ.
Average	F	61.4	56.5	4.0	175/93	8 A.F.	512	
	M	58.0	54.5	3.5	146/88	3 A.F.	592	
Clinical cases—private								
1	F	43	38	5	150/78	Sinus		
2	F	54	53	1	144/90	Sinus		
3	M	51	42	9	180/90	A.F.		Cor. occ.
4	F	53	38	15	134/85	Sinus		Cor. occ.
5	F	53	52	1†	190/120	A.F.		
6	F	82	81	1	125/78	Sinus		
7	M	69	63	6†	138/100	A.F.		
8	F	57	55	2	130/80	Sinus		Cor. occ.
9	F	50	49	1	156/88	Sinus		
10	F	54	50	4†	195/110	Sinus		Cor. occ.
11	F	58	50	8†	180/90	Sinus		Cor. occ.
12	M	48	45	3	128/78	Sinus		
13	M	52	50	2	148/88	Sinus		
14	F	49	40	9†	130/100	Sinus		
15	F	34	29	5	124/86	Sinus		
16	F	31	21	10	118/80	A.F.		
17	F	56	50	6	136/80	Sinus		
Average	F	51.8	46.6	5.2	147/89	2 A.F.		
	M	55.0	50.0	5.0	148/89	2 A.F.		

* Age is at death or when last observed clinically.

† Indicates known fatalities.

TABLE 1—*Concluded*

	SEX	AGE*	ONSET OF A.P.	DURATION OF A.P.	B.P.	RHYTHM	WT. OF HEART	OCCURRENCE OF COR. OCCLUSION
Clinical cases—Outdoor department								
1	F	65	63	2	180/100	Sinus		
2	M	65	60	5	170/80	A.F.		
3	F	41	40	1	130/78	Sinus		
4	F	44	43	1	140/72	Sinus		
5	M	60	58	2	180/110	A.F.		
Average	F	50.0	48.7	1.3	150/83	0 A.F.		
	M	62.5	59.0	3.5	175/95	2 A.F.		
Total								
26	F	55.3	50.4	4.3 yr.	158/90	10 A.F.		10 cor. occ.
12	M	57.7	53.7	4.0 yr.	152/89	7 A.F.		

marked anemia were excluded (except 1 case) in order to eliminate any complicating factors that might be responsible for the anginal state.

There were 314 cases of mitral stenosis examined post mortem at the Peter Bent Brigham Hospital between 1913 and 1940 which had no other significant valvular disease. Of these, 16 or 5 per cent had definite coronary artery disease, 15 having angina pectoris and 1 showing a myocardial infarct on post-mortem examination without a clinical history of angina during life. This is a higher incidence of a combination of coronary artery disease and mitral stenosis than is seen in ordinary practice, for in a series of 741 definite cases of mitral stenosis observed in private practice 17 or 2.2 per cent had angina pectoris in conjunction with mitral stenosis. To these 33 cases were added 5 instances of combined mitral stenosis and angina pectoris followed in the outdoor department of the Peter Bent Brigham Hospital. These 38 cases of mitral stenosis and angina pectoris were used as the basis for this review. For the most part, average figures will be discussed of the entire group of 38 cases. However, where there are significant differences in the observations of the hospital cases that were examined post mortem and those seen in private practice, separate comments will be made.

RHEUMATIC HISTORY

Of the 38 cases, 17 (44.7 per cent) gave a definite history of previous rheumatic fever or chorea. This is similar to what has been found in large series of cases of mitral stenosis in which a history of early rheumatic infection can only be obtained in slightly more than 50 per cent of the cases.

AGE AND SEX

The age distribution in the 16 cases studied post mortem ranged from 50 years to 69 years, with an average of 60 years. In the clinical group, the

ages when last seen varied between 31 and 82 with an average of 53.1 years. There were 26 females and 12 males, a ratio of more than 2 to 1. This proportion is quite remarkable when it is considered that angina pectoris in the general population occurs much more commonly in males (3 to 1). The combination of mitral stenosis and angina pectoris is the only appreciable group of patients with angina in which females predominate.

OCCURRENCE OF ANGINA PECTORIS

In the cases studied at autopsy, the age at which angina pectoris or coronary occlusion first occurred varied between 47 years and 68 years, the average being 57 years in the female and 55 years in the male group. The duration of angina varied between 1 and 15 years, the average being 4 years in the female and 3.5 years in the male. In the 11 cases in which cardiac failure occurred, it began at an average age of 54 years. In 5 of these 11 cases, angina first appeared after the initial symptom of dyspnea; in 2, angina was evident before the onset of dyspnea; and in 4 cardiac failure and angina made their appearance at the same time.

Of the 16 cases observed post mortem, 5 had coronary occlusion. Two of the 5 had a previous history of angina, 2 did not, and 1 case was not diagnosed as having coronary occlusion during life although this was found at necropsy. It is not known how many of the cases of angina would have shown occlusion of the coronary arteries if the technique of Schlesinger (3) had been used.

In the clinical cases, the age at which angina first began varied between 21 and 81 years, the average being 48.3 years, with females about three years younger than males. The duration of angina varied between 1 and 15 years, the average being about 5 years in both sexes. Two of the cases had coronary occlusion with angina thereafter, while 3 had a coronary occlusion following the angina. Of the 22 clinical cases, 5 patients subsequently died, the average age at death being 57 years, i.e. 8 years on the average after the onset of the angina. In general it appears that angina pectoris and coronary occlusion occur in the same manner in this group of patients with mitral stenosis as in those without valvular disease. The anginal state may precede or be initiated by coronary thrombosis. It is of some interest that in a significant number of instances, angina first developed after the onset of congestive failure.

BLOOD PRESSURE CONSIDERATIONS

The average blood pressure in the 16 cases studied at autopsy was 164 systolic and 91 diastolic. The range varied from a highest systolic reading of 250 and highest diastolic of 110 to a lowest systolic of 105 (following a coronary thrombosis) and a lowest diastolic of 70. Only 4 of the 16 had a systolic pressure over 200 while 5 had diastolic pressures over 100. The average pressure for the 10 females was 175 systolic and 93 diastolic, and the readings for the 6 males were 146 systolic and 89 diastolic. The

average reading in the 17 private clinical patients was 147 systolic and 89 diastolic. The higher levels in the series studied at autopsy might be explained by the fact that the average age in this group was seven years older than in the clinical group. The average blood pressure of the 12 females was 147 systolic and 89 diastolic and for the 6 males was 148 systolic and 89 diastolic. The tendency for the females to have a higher blood pressure is in accord with findings obtained in a study of ordinary angina pectoris cases (4) although the difference is not so great.

PHYSICAL FINDINGS AND CAUSE OF DEATH

All of the 38 cases had an apical diastolic murmur and 28 had an apical systolic murmur as well. Seventeen of the 38 (45.0 per cent) had permanent auricular fibrillation, confirmed by electrocardiograms in twelve instances. One showed left bundle branch block in the electrocardiogram. Of the 16 studied post mortem, the cause of death proved to be congestive failure in 6 instances, 3 died of cerebral hemorrhage, 2 of cerebral thrombosis, 2 of infarct of the lung and 2 as a direct result of coronary occlusion. One patient died as a result of bronchopneumonia.

NECROPSY FINDINGS

Sixteen of these cases were examined post mortem. The weight of the heart varied from 390 grams to 900 grams, with an average of 542 grams. The average weight of the heart in the 10 females was 512 grams and in the 6 males it was 592 grams. The mitral valve showed definite stenosis in every instance. Four had the characteristic "fishmouth" deformity, while 3 others were classified as "quite marked." Special interest was taken in the description of the gross and microscopic examination of the coronary arteries. In 3 no significant arteriosclerosis was observed. Three had slight, 4 had moderate, and 5 had marked coronary sclerosis. In 1 no dissection of the coronary arteries was possible because of the fused layers of the pericardium. In 3 of the 16 cases, there were mural thrombi in the right auricle, 1 having thrombi in the left auricle and right ventricle as well. The following are brief abstracts of the three cases of angina and mitral stenosis showing no significant coronary artery sclerosis.

CASE REPORTS

Case 1. History. A 55 year old woman entered the Peter Bent Brigham Hospital for the first time in 1917. For the previous 12 to 14 years she had moderate dyspnea on exertion and some palpitation. These symptoms were accentuated after a severe cold seven months before entry. Following this, she continued to be in moderate failure until she finally required hospital care. Her past history revealed that she had chorea as well as frequent sore throats in childhood.

Examination. The heart was enlarged to the left and right. A systolic and apical diastolic murmur was heard, the rhythm was grossly irregular. There were râles at both bases, but no peripheral edema. The blood pressure was 160 systolic and

94 diastolic. On adequate cardiac therapy the patient improved and was discharged after 27 days.

Course. She was again in the hospital for three weeks in June, 1920 for troublesome dyspnea. The electrocardiogram showed right axis deviation and auricular fibrillation. It was otherwise normal. The only change was enlargement of the liver.

The patient's next admission was in February, 1921. She had the same symptoms as before except that now she complained of definite substernal pain radiating to the left shoulder, coming on after exertion and relieved by rest. The character of the pain was quite typical of angina. She was in moderate failure, but responded well to cardiac therapy and was discharged home only to return five months later because of marked dyspnea, swelling of the abdomen and cough. The substernal pain was present, but not as severe as before, inasmuch as she had not been able to exert herself. At this time her blood pressure was 140 systolic and 90 diastolic. The heart action was grossly irregular and the first heart sound was replaced by a harsh, loud, long systolic murmur. There was no definite diastolic murmur heard at this time. There were many moist râles at both lung bases. The patient failed to respond to therapy and died two months later.

Necropsy findings. The mitral valve was quite rigid, stenosed and calcified. No other valves were involved. Both right and left ventricles were hypertrophied. The heart weighed 560 grams. There was a mural thrombus in the right auricle. Grossly and microscopically the coronary arteries showed no significant arteriosclerosis.

Case 7. History. A 50 year old woman was admitted to the hospital in March 1936. She stated that she had been well until two years before entry when she noticed slight dyspnea on exertion. This was not severe, however, and not until one and a half months before entry did her symptoms demand medical attention. At this time her local physician administered digitalis which gave her some relief. However, the week before admission, she became dyspneic at rest, orthopneic, had peripheral edema, nausea and vomiting.

The family history was non-contributory, and the past history revealed that the patient had migrating joint pains at the age of 24.

Examination. The patient was a cyanotic, orthopneic woman with pulsating neck veins, enlargement of the heart to the right and left, grossly irregular heart rhythm, apical systolic and diastolic murmurs, râles throughout both lungs and peripheral edema. The blood pressure was 200 systolic and 95 diastolic. Positive blood Wassermann and Hinton tests were found. An electrocardiogram showed auricular fibrillation but was otherwise normal. She improved on cardiac therapy and left the hospital 28 days after admission.

Course. She returned to the hospital in November 1938. At that time she complained of severe chest pain radiating to the left arm, coming on after exertion and relieved by rest. The pain was typical of angina pectoris, occurring two to three times a month. In addition, during the month prior to entry she had suffered marked increase in dyspnea and peripheral edema. The physical findings were unchanged. She failed to respond to adequate cardiac therapy and on the twenty-ninth hospital day, developed signs and symptoms of pneumonia of the upper lobe of the right lung and died a day later.

Necropsy findings: Lobar pneumonia and a stenosed mitral valve that barely admitted the tip of one finger were disclosed. The aortic valve was not involved. The heart weighed 480 grams and the myocardium was slightly thicker than normal in all chambers. The coronary arteries were patent and there was no significant coronary sclerosis, grossly or microscopically. There was no evidence of syphilis in the heart or aorta.

Case 10. History. A 57 year old woman was first seen in the Peter Bent Brigham Hospital on February 6, 1933. For the previous eight years, she had had dyspnea and attacks of substernal pain radiating to the left arm after moderate exertion and relieved by rest. The type of pain was characteristic of angina pectoris. Five years before admission she first noticed that her ankles became swollen. Following this, the patient complained that the dyspnea and palpitation had become more marked, peripheral edema more prominent and attacks of substernal pain more frequent, so that she finally was forced to seek medical advice.

The family history revealed that the patient's father died at the age of 45 from "heart disease". There was no history of rheumatic fever, but the patient had frequent attacks of tonsillitis as a child.

Examination. At the time of admission the blood pressure was 170 systolic and 100 diastolic. The heart action was grossly irregular, the first sound was slightly accentuated and there was a short, faint, whistling systolic murmur and a definite mid-diastolic rumble at the apex. There were a few moist râles at both lung bases, a large tender liver and moderate peripheral edema. An electrocardiogram, revealed auricular fibrillation, but it was otherwise normal.

The patient improved on bed rest, phlebotomy and digitalis therapy and was discharged 22 days after admission. She was readmitted to the hospital nine months later with essentially the same complaints except that the anginal pain was much more severe and frequent. Physical examination at that time was unchanged except that the blood pressure was 210 systolic and 110 diastolic and there was definite evidence of fluid in both pleural cavities. The patient again improved somewhat on cardiac therapy, but 21 days after admission she had signs of a cerebral thrombosis in the right hemisphere, developed acute pulmonary edema and died 12 hours after the onset of these symptoms.

Necropsy findings. In addition to the cerebral thrombus and the pulmonary edema, the heart weighed 520 grams. The mitral valve was "fishmouth" in type. No other valves were involved. Grossly, the coronary arteries were not occluded or significantly narrowed. Microscopically there was only a moderate degree of intimal proliferation and some adventitial proliferation at various points. No thrombi were found.

DISCUSSION

In the study of any large group of adults, it is evident that a significant number of cases of coronary artery disease will be found. If a thousand patients with chronic arthritis or peptic ulcer were to be reviewed, it would not be surprising if an appreciable proportion would be found to have angina pectoris. Similar findings must result if a review of patients suffering with mitral stenosis were made. The question that arises, however, is whether angina pectoris is unduly frequent in cases of mitral stenosis and if so what may be the factors that account for this increased frequency. Is there something peculiar about the lesion of mitral stenosis that will produce the anginal state? If the frequency of these two conditions is more than coincidental, the following three findings should be present. One would expect to find a larger incidence of angina in cases of mitral stenosis especially during the early decades than in the average population. The average age at death of such cases should be lower than that of cases of angina in general. Finally a larger number of cases of mitral stenosis and angina should have no significant coronary artery disease.

Concerning the first point, we know of no statistics indicating the occurrence of angina pectoris and coronary artery disease in the general population at various ages. For that reason, it is difficult to estimate what the occurrence of angina in the various decades amongst patients with mitral stenosis would be. As to the second supposition mentioned above, there are some data available. The average age at death of 100 consecutive cases of classical angina pectoris was found to be 60.7 years for men and 62.7 years for women (4). It is significant that in the 21 fatal cases in this study including 16 examined post mortem, the average ages at death were 59.6 years for the men and 59.1 years for the women. Concerning the occurrence of angina in the younger decades with and without mitral stenosis, it is also difficult to make comparisons. The published incidence of cases of angina under 40 years varies a great deal. White (5) found that 2.3 per cent had their first attack of angina under the age of 40. In a similar analysis, Herrick quoted by White (5) found 8 per cent of 200 cases were under 40 years. In a more extensive review (6) of 3376 patients with coronary artery disease, 1.5 per cent developed first symptoms before the age of 40. In contrast, amongst the 38 cases of mitral stenosis here analyzed, three cases had definite angina before the age of 40. This series is much too small to be conclusive, but it suggests that angina is unduly frequent in the early decades when patients also have mitral stenosis and that patients with both angina and mitral stenosis (especially women) die at a slightly younger age (59.1 years) than when angina alone is present (62.7 years). Inasmuch as mitral stenosis *per se* is a major cause of early death, this discrepancy is not surprising. It does not, however, prove that the mitral stenosis was in any way the cause of the angina which was present. If the patients with the two conditions had lived as long or longer than those having simple angina, it would have served as convincing evidence that there is no causal relationship between mitral stenosis and angina.

In investigating the occurrence of angina without significant coronary artery disease, 3 cases were found amongst the 16 examined post mortem. There were three additional cases still living who first had angina at the ages of 21, 29, and 38 respectively. The early ages at which angina developed in these latter three cases make it likely that significant coronary artery disease was absent. There is, therefore, a total of 6 cases out of 38 with essentially normal coronary arteries which is a much greater incidence than is found in ordinary cases of angina pectoris. Other authors have reported similar experiences. Kouretas in 1924 quoted by Blackford (7) reported three instances of angina with mitral stenosis in which post-mortem examination showed no coronary artery disease. Five additional cases have more recently been reported (7, 8, 9, 10) ranging in age from 17 to 36 years. The very recent introduction of the Schlesinger technique of studying the coronary arteries throws some doubt on the negative findings previously reported, because with this new method small but significant

areas of occlusion can be detected that would otherwise be entirely overlooked. But even with this method, Blumgart and Schlesinger (11) found one instance of mitral stenosis in which they believe that the angina which was present was not the result of minor changes in the coronary arteries which were found. Although the question remains somewhat inconclusive, the data presented above strongly suggest that the association of angina and mitral stenosis is more than coincidental.

It is not our purpose to review the intricate problem of the mechanism of anginal pain. The prevailing opinion is that in one way or another, anginal pain is due to relative myocardial anoxemia, i.e. a question of demand and supply to the heart muscle. When major changes were present in the coronary arteries in this group of cases of mitral stenosis, no other factor was necessary as an explanation of the anginal state. When such changes were not present, however, one might ask whether there was anything peculiar about mitral stenosis itself or its secondary effects, like diminished cardiac output, dilatation of the auricles etc., that would be conducive to the production of anginal pain. It has been suggested (8) that the pain is due to compression of the left coronary artery between the left auricle and pulmonary artery or to the compression of the aorta and the aortic plexus by a dilated left auricle. Hochrein (10) found a narrowing of the mouth of the left coronary artery which was pulled downward by the deformed anterior cusp of the mitral valve, which in turn was held down by a shortened chorda tendinae in a case of mitral stenosis. He offered this as an explanation for the angina which was present. Further careful anatomical study along similar lines is much needed. Another explanation that has attracted attention is that the angina is due to a rheumatic involvement of the coronary arteries. Karsner and Bayless (12) went so far as to say that rheumatic fever regularly produced disease of the coronary arteries but that, except for the presence of Aschoff nodules, these lesions were not specific for rheumatic fever and might be produced by other infectious diseases. We do not subscribe to this view as an explanation of the occurrence of angina because if it were so, angina would be a prominent feature in patients who have or have had rheumatic fever and do not have concomitant mitral or aortic valvular disease, which is not the case.

In summarizing our experiences with this problem, it would seem that angina occurs more frequently in cases of mitral stenosis and at a younger age than in the general population, and when it does so is more often unassociated with significant coronary artery disease than in the ordinary case of angina without valvular disease. The explanation of the anginal pain in those cases of mitral stenosis that show no significant coronary artery disease is still in doubt, although in some way it probably depends on a disproportion between coronary blood flow and the work of the heart. In most cases, however, the pathological changes in the coronary arteries are sufficient to account for the occurrence of angina pectoris.

SUMMARY AND CONCLUSIONS

1) A study was made of 38 cases having both mitral stenosis and angina pectoris, 16 of which were examined post mortem.

2) It was found that 17 of 2832 cases of coronary artery disease seen in private practice had mitral stenosis i.e. 0.6 per cent.

3) These 17 cases of mitral stenosis with angina or coronary thrombosis were observed amongst 741 consecutive cases of mitral stenosis, i.e. 2.6 per cent.

4) The incidence of significant coronary artery disease amongst 314 cases of mitral stenosis examined post mortem was 5 per cent.

5) The average age for the onset of angina was 50.4 years for women and 53.7 years for men, the duration of angina being about 4 years in both sexes.

6) Whereas in ordinary cases of angina men predominate about 3 to 1 and die at a younger age, in these cases of angina and mitral stenosis women predominate 2 to 1 and die at a younger age.

7) Amongst the 16 cases examined post mortem, the average blood pressure of the women was 175 systolic and 93 diastolic, and for the men 146 systolic and 88 diastolic. The blood pressure for the other cases was somewhat lower.

8) Seventeen cases had permanent auricular fibrillation. In 5 of the 11 that had congestive failure, angina developed after the initial symptom of dyspnea.

9) Three of the 16 cases examined post mortem showed no significant pathological changes in the coronary arteries.

10) The finding of normal coronary arteries in these 3 cases and in 9 similar cases reported by other observers indicates that in mitral stenosis factors other than coronary sclerosis may be responsible for the occurrence of angina pectoris.

•11) In the great majority of instances, however, when mitral stenosis and angina coexists, the two conditions are independent of each other, the former being due to rheumatic infection and the latter the result of ordinary coronary artery sclerosis.

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PAROXYSMAL AURICULAR FIBRILLATION AND FLUTTER WITHOUT SIGNS OF ORGANIC CARDIAC DISEASE IN TWO BROTHERS

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The occurrence of paroxysms of auricular fibrillation in patients without other evidence of heart disease is uncommon; paroxysmal auricular flutter, under these circumstances, is a rarity (1 to 4). Only once before, as far as could be determined, has reference been made to the familial incidence of this type of arrhythmia which is dependent upon the presence of a circus movement. In their paper on "Uncomplicated Auricular Fibrillation and Auricular Flutter," Orgain, Wolff and White mentioned in a footnote that three of their patients with fibrillation were brothers (4). Although it was stated that these cases would be described in detail in a later report, this was never done (5). The two brothers whose case histories are here given have been under observation for 9 and 7½ years respectively. One of them, at the age of 59 years, experienced his first paroxysm of auricular flutter; the other, when 48 years old, was for the first time conscious of a cardiac irregularity. In neither has it been possible to detect any signs of organic heart disease.

CASE REPORTS

Case 1. History. Mr. X, a retired stockbroker, was first seen in November, 1932, when he was 59 years of age. He complained of jumpiness of the heart which had been present for 10 days.

His father died at the age of 69 of apoplexy. His mother died of tuberculosis of the throat and lungs, at the age of 62. One brother (Patient Y in this paper) and 2 sisters were living and well. One brother died suddenly at the age of 48, presumably of coronary disease.

A tuberculous left kidney was removed when the patient was 40. A sinus tract persisted for some months and he took the sun cure in Leysin, Switzerland. A secondary operation was successful in healing the wound and there was no further trouble with the urinary passages. He had dry pleurisy at the age of 29, and pneumonia at 31. He was in the habit of taking setting-up exercises every morning and could walk for from four to six miles without discomfort. He frequently played eighteen holes of golf and was able to jog a mile without undue dyspnea. He took two cups of coffee each day and smoked three or four pipes and one cigar. He drank a cocktail before dinner and a whiskey and soda with his evening meal.

Present illness. A year ago, after exhibiting in a horse-show, he felt poorly. His physician found the systolic blood pressure to be 180 mm. Hg. but the hypertension subsided promptly. He was then well until 10 days before I first saw him. He had

again taken part in a horse-show in which he drove a coach with horses which he had not previously handled. After he had completed his performance he realized suddenly that his heart was going very fast, but regularly. This type of tachycardia lasted from 10 P.M. to 5 A.M. the following morning; then the beat became irregular and at intervals was slow. He remained at home during the following week, though not in bed. His heart was still irregular and thumped to such a degree that it shook his whole body.

Examination. The patient was a tall, well-built, healthy looking man. The veins of the neck were a little full and showed typical flutter waves. The lungs were clear. The heart was not enlarged on percussion. The rate was 92; the rhythm was quite irregular. The sounds were of fair quality. A short systolic blow was heard at the apex. The peripheral vessels were not thickened. The blood pressure was

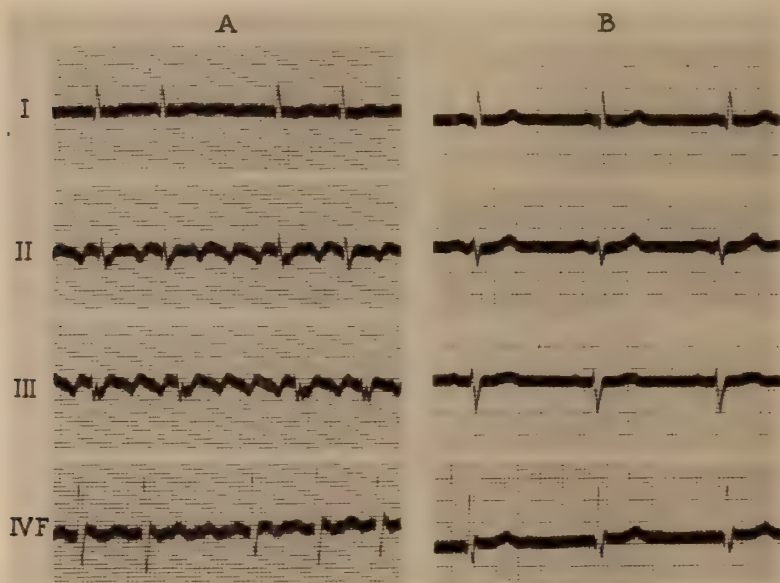


FIG. 1. Electrocardiograms of Case 1. A, paroxysm of auricular flutter. B, regular sinus rhythm.

146 systolic and 96 diastolic. The left lumbar kidney incision was well healed and there were scars also in the left groin.

Fluoroscopic examination showed no cardiac enlargement. The aorta was a little dilated and tortuous, but no more so than might be expected at this age. The electrocardiogram (fig. 1) showed auricular flutter with auricular rate of 280 and ventricular rate of 82. The degree of block varied from two to one to four to one. The urine contained neither albumin nor sugar. There was an occasional leucocyte in the sediment.

Course. The patient was put to bed for two weeks and the administration of digitalis was begun. In the course of ten days he was given 3.4 Gm. (34 cat units). The ventricular rate was slowed to 68; the auricular rate was unaffected. Digitalis was continued and he was finally permitted to get up. On January 24, 1933, quinidine was begun and was given in full doses. This was ineffectual in changing the cardiac rhythm. Digitalis was then resumed and he was permitted to be up and about.

The ventricular rate was maintained between 60 and 70 beats per minute. He was able to walk for as much as four miles without discomfort. Frequent electrocardiograms were taken during the next eight months. All showed auricular flutter with varying degrees of auriculo-ventricular block.

On July 15, 1933 (nine months after the onset of the arrhythmia), the patient once again drove a four-in-hand. Immediately after getting off the box he noted that the irregularity had completely disappeared. He was acutely aware of the change. Since then, he had occasionally been conscious of his heart beat at night, but there was no return of the cardiac irregularity.

He was not seen again until February 16, 1934. At that time he looked well. The heart rate was 68. The rhythm was regular save for a very occasional premature beat. The blood pressure was 156 systolic and 92 diastolic. He was encouraged to lead a normal and unrestricted life. In December, 1936, at the age of 63, he married.

He was next seen on September 21, 1938. He stated that on July 9, of that year, while driving from the first tee at a summer resort, he had sudden substernal pain. He was immediately put to bed and it was thought by the local physician that he had had a coronary occlusion. He was kept in bed for twelve weeks. There was no fever or leucocytosis. The blood pressure remained low—a little over 100 systolic. The electrocardiogram showed auricular flutter. He was given small amounts of digitalis without change in the rhythm and was finally taken home in an ambulance. When I saw him the ventricular rate was 78. Auricular flutter was still present. The blood pressure was 128 systolic and 78 diastolic. Digitalis was begun and on October 20 (a little over three months after the onset of flutter) he began to fibrillate. Six days later, normal rhythm was resumed. He was again conscious of the change. A daily maintenance ration of 0.1 Gm. of digitalis was continued.

On December 3, 1938, while playing cards, the heart suddenly began to beat rapidly and irregularly. When I saw him a little later, the apex rate was 112 and I was under the impression that the auricles were fluttering. He was given morphine by hypodermic injection, but slept poorly. The following morning the rhythm was totally irregular and an electrocardiogram showed auricular fibrillation. A few doses of quinidine promptly restored normal rhythm. He was then given quinidine, 0.2 Gm. three times a day and, with the exception of short intervals, has taken it ever since. There was one brief attack of flutter which began on August 6, 1939. This was followed by auricular fibrillation and on September 2, the resumption of normal rhythm. Since then there has been no recurrence of either flutter or fibrillation. There have been occasional premature beats. He is now 68 years of age. He plays from nine to twelve holes of golf without dyspnea or fatigue and swims in the ocean during the summer. The heart rate is usually in the fifties. The blood pressure on the last examination was 142 systolic and 84 diastolic.

Case 2. History. Mr. Y, a brother of Mr. X, was a stockbroker and was first seen in July, 1934. At that time he was 58 years of age.

He had had typhoid fever at the age of 37. His appetite was large and he enjoyed good food. He had noted that lobster, cucumbers, melon and radishes did not agree with him, but he liked all of them. He had rowed on his college crew and up to five years before had played polo. At this time he was playing golf and doubles at tennis. He swam for short distances. He did all of these things without dyspnea or cardiac pain. He smoked two cigars a day, took three cocktails before dinner and wine with the evening meal.

Present illness. For ten years, at intervals, he had noted occasional attacks of irregular beating of his heart, especially after overeating. The nature of the arrhythmia was not then known. The items of food previously mentioned were partic-

ularly apt to induce a paroxysm. He was unaware of any other exciting cause. For many years also he had noted dizziness after a sudden change of posture; on several occasions he fainted. For six years he had had attacks of asthma which came on irregularly, usually after shaving in the morning. Many tests for allergy were negative. However, since giving up shaving with a brush and removing certain powders from the bathroom, the attacks ceased. His heart had been repeatedly examined and was found normal. The purpose of his visit was to find out if he might continue to exercise.

Examination. Like his brother, Mr. Y was a tall man, of athletic build. There was slight retinal sclerosis. The heart was not enlarged. The rhythm was regular; the rate 88. The sounds were normal and clear. The blood pressure was 116 systolic and 72 diastolic.

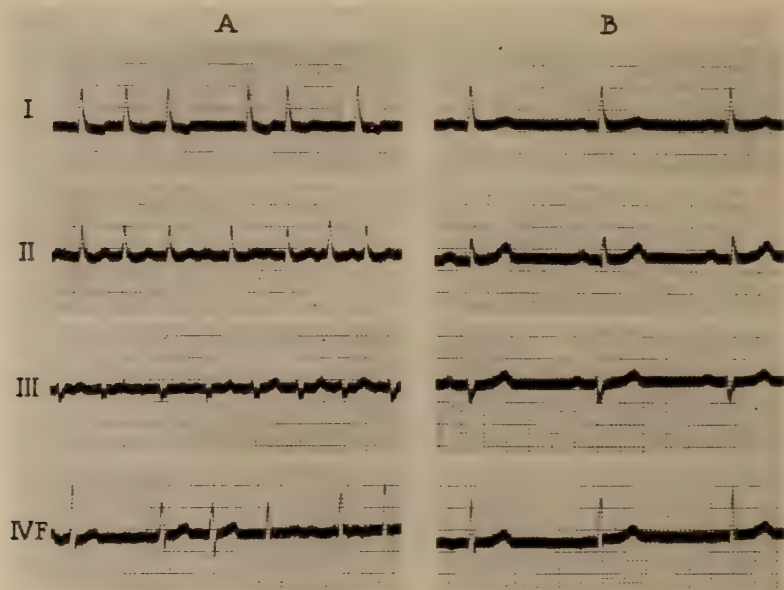


FIG. 2. Electrocardiograms of Case 2. A, paroxysm of auricular fibrillation. B, regular sinus rhythm.

Fluoroscopy was attempted, but as soon as the room was darkened the patient became pale, broke out in a profuse sweat and sank to the floor in a faint. There was no change in heart rate. After inhaling the fumes of aromatic spirits of ammonia, he promptly regained consciousness and three minutes after the syncopal attack the heart rate was 88, the blood pressure 126 systolic and 76 diastolic. The electrocardiogram was normal (fig. 2). He was advised to avoid the items of food which caused indigestion, as well as to eat and drink moderately.

Course. He was not seen again until June, 1937 (three years later), after his left kidney had been removed because it contained an adenocarcinoma. There was a brief bout of auricular fibrillation on the day following the operation; the arrhythmia disappeared promptly after the administration of digitalis. After convalescence he resumed tennis and felt extraordinarily well.

The patient was seen at intervals during the next four years. He was advised to take quinidine, 0.2 Gm. three times a day, but did so irregularly. He had several attacks of fibrillation, but I saw him in only four of these. One paroxysm followed a

severe attack of gripe. Another came on at two-thirty in the morning after eating a late supper and drinking a good deal of beer after the theatre. On another occasion, an attack came on after a heavy meal. He felt faint during the screen version of "Gone with the Wind". Between attacks he was remarkably well.

He was last seen early in 1941. The heart rate was 56; the rhythm regular. The sounds were a little distant and clear. The blood pressure was 118 systolic and 74 diastolic. He was taking quinidine regularly. There was no evidence of recurrence of the renal neoplasm. He was then 65 years old and because of his age and history, was advised not to play tennis and to confine his exercise to golf and riding.

COMMENT

These two brothers were remarkably alike in many respects. Both were tall, well-built and athletic. Both had been stockbrokers. Although externally calm and even-tempered, they were unusually sensitive to emotional experiences. Each lost his left kidney by surgical operation, one because of tuberculosis, the other because of carcinoma. The attacks of arrhythmia began late in life—in the first case at the age of 59, in the second at the age of 48. The form of the electrocardiogram during periods of sinus rhythm also showed features of similarity. In both instances the continuous administration of quinidine was effectual in preventing the recurrence of paroxysms.

The duration of auricular flutter for nine months in Mr. X, its refractoriness to drugs during this period and the spontaneous resumption of normal rhythm, recall to mind the remarkable case of Sprague and White (6). A machinist, aged 49 years, suffered from persistent flutter for five years, in spite of the use of digitalis and quinidine in full dosage. At the end of that time, for no apparent reason, regular sinus rhythm recurred. No evidence of organic cardiac disease was discovered.

The benign course of auricular fibrillation and flutter in patients without signs of anatomic changes in the heart has been pointed out by numerous observers (1 to 4, 7). The prognosis is particularly good when the arrhythmia is of the paroxysmal type. The immediate cause for the onset of attacks has been variously ascribed to effort, emotional stress, infection, the action of some toxin, or digestive disorders. In the case of Mr. X, the excitement of exhibiting in a horse-show appeared to be responsible not only for initiating flutter but for terminating the circus movement. The second attack followed immediately after driving a golf ball. The third occurred during a close game of bridge. Mr. Y's attacks of fibrillation were induced usually after eating and drinking more than he should, and particularly when he ate articles of food which he knew disagreed with him. In one instance a paroxysm followed a surgical operation (nephrectomy); on another occasion, it occurred during a severe attack of gripe.

It is not known what basic conditions render certain persons susceptible to such cardiac upsets. The familial incidence suggests the possibility that constitutional factors may be concerned; but what these are, is en-

tirely a matter of conjecture. Perhaps there exists an unusually delicate balance between the sympathetic and parasympathetic control of the heart, and hence this is readily disturbed. Certainly it seems more likely that a nervous mechanism is responsible for "pulling the trigger" than that the irregularity results from some intrinsic defect in the myocardium. Experiments in animals have shown that the sympathetic centers in the hypothalamus exert an effect upon cardiac rhythm (8, 9). Why the tendency for the appearance of a circus movement in the auricles should manifest itself in these two patients only in the fifth and sixth decades of life is not clear. Conceivably, vascular changes may have developed in the hypothalamic area, rendering it more sensitive to stimuli which previously were below the threshold of response. But the defect which initiates the paroxysms has not been demonstrated and remains obscure.

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FIVE YEARS OF CANCER RESEARCH

A RETROSPECT

RICHARD LEWISOHN, M.D.

[Consultant Surgeon to The Mount Sinai Hospital]

My dear Ben,

I have been thinking a good deal about the selection of a subject for this commemorative volume. I might have presented some clinical subject dealing either with blood transfusion or some gastroenterological problem, subjects which have interested me during my thirty years on the Surgical Service of The Mount Sinai Hospital. Or I might have selected some presentation from our joint goitre service, which we organized a number of years before my retirement from active service. However, I have decided to discuss today the development of the Cancer Research Laboratory at The Mount Sinai Hospital.

I feel that such a presentation is very timely in this volume. You have always shown a keen interest in the problems of research, even if they are somewhat far away from the road of clinical medicine *sensu strictiori*. We have always agreed that a doctor who just attends to the care of patients, without doing some productive work in medical research, misses a great opportunity. He not only fails to make full use of the possibilities which medicine offers to its pupils in such abundant fashion, but also he is derelict in his duties towards the institution which he serves and which offers him ample facilities for adding a small stone here or there to the mosaic of medical progress. After all, most of us agree that the reputation of a great hospital is made not only by the proper care of the patients—all modern hospitals perform that function admirably—but also by important contributions of its members to medical research. By doing so they may advance the clock of human accomplishments and thus help to diminish the great reservoir of human suffering.

In fact in many hospitals, and especially in university clinics, the trustees have ruled that no member of the medical profession should occupy a leading position on the staff and no junior member may expect promotion, unless he has demonstrated ability for progressive research work.

The cancer research laboratory started five years ago in very humble beginnings. Through the courtesy of Dr. Shwartzman I had been allowed the use of a few cancer mice for testing a spleen extract prepared for me by Dr. David Klein, chief chemist of the Wilson Laboratories.

It may interest you to hear why I selected the spleen for my work.

The explanation for this step was my complete ignorance of the experimental cancer literature. I had often observed at surgical operations that in general abdominal carcinomatosis the spleen was usually free from any metastasis. It may amuse you to know that when I started the experimental work with the spleen extract I had the wrong impression that this observation had never been used in experimental cancer research. However, when I began to study the literature I found that the spleen had been used extensively for many years by many investigators. Thus I started the work because I was not familiar with the literature on experimental cancer research. Sometimes it seems to be an asset not to know too well the work of others. If I had been familiar with the many previous failures of experimental splenic therapy I might never have taken up this line of research.

Before I started this problem I gave careful consideration to the question of the selection of the proper tumor for testing the spleen extract. As you know we have two different types of mouse or rat tumors at our disposal for experimental work, namely transplanted or spontaneous tumors. Experiments with any new form of cancer treatment should be started on transplanted tumors, as large numbers with tumors of this type are easily obtainable. After its therapeutic efficacy has been proven on transplanted tumors, the new procedure should be tested on spontaneous tumors, for if complete regressions are obtained in transplanted tumors, the same therapy *may* show results in spontaneous tumors. However, if a therapeutic attempt fails in transplanted tumors, spontaneous tumors will not respond to that treatment.

After consultation with Dr. William H. Woglom (whose help and advice has been of inestimable value to our laboratory during these five years) I selected Sarcoma 180 for a test of the spleen extract. Sarcoma 180 is a malignant tumor which can be transplanted at ease in certain mice strains. A small piece of malignant tumor tissue is introduced subcutaneously with a trocar. After eight or ten days this minute piece of tissue will have grown to considerable size, and the treatment can start. Naturally it is important for any work with transplanted tumors to keep identical numbers of untreated control animals for observation of spontaneous regressions. I found that spontaneous regressions in Sarcoma 180 ranged about 8 per cent.

The injections of spleen extract were given subcutaneously, far away from the tumor, in order to avoid the possibility of direct action.

As I told you, the first experiments were given to a few animals only. You may imagine my surprise and satisfaction when some of these tumors showed a complete change of appearance on the day following the treatment. The tumor showed extensive hemorrhages very similar to the appearance of these tumors after treatment with Shwartzman's bacterial filtrates. Under daily treatment a number of tumors disappeared completely.

I have described these first experiments in detail, as they induced me to continue my interest in this problem and to expand the facilities for careful further investigation.

After the work had continued for about six months, I was very fortunate in associating with me Mrs. Leuchtenberger. Her imagination and enthusiasm, her excellent training in chemistry, bacteriology and biology made her an ideal collaborator. A few months later Dr. Leuchtenberger joined the organization as pathologist. During the last three years Dr. Laszlo has been biochemist. A great deal of the progress which has been made in the purification of our extracts is due to his endeavours. Dr. K. Bloch spent one year with us, cooperating with Laszlo in the chemical laboratory. He recently returned to the College of Physicians and Surgeons and was replaced by Dr. Dische.

Two technicians and two animal attendants complete the organization, comprising a staff of nine people. Our mouse colony has grown from the original dozen mice to over 2000 animals. We now have two large laboratories, one for biology and pathology, the other for chemistry.

I have dwelt somewhat in detail on the physical growth of the Cancer Research Laboratory. It seems of interest that such an organization could be formed in the short period of a few years, in spite of the limited facilities of space in The Mount Sinai Hospital. I have always appreciated the understanding and the cooperation which I received from the Board of Trustees.

Let us return now to a further review of the scientific work. After we had established complete disappearance in 60 per cent of the animals with Sarcoma 180, we had to prove that this was due to a specific action of the spleen extract. Four other organ extracts, prepared exactly like the spleen extract, were tested, namely liver, heart, pancreas and testis. None of these extracts influenced the normal growth of Sarcoma 180 in the slightest degree. It would carry us too far to discuss here the many other tests which were performed, before we were sure that the spleen extract presented a specific action.

A possible lead to the action of the spleen extract upon the tumor may be found in the following observation: The spleen in the controls and in animals treated with other organ extracts was small, whereas the spleens in the animals which had been cured of their Sarcoma 180 by treatment with spleen extract was very large, often four to five times the normal size. This interesting observation was the basis for an important advance in our research problem. An extract was prepared from these enlarged spleens. This extract was injected intravenously into mice (Strain A, Jackson Memorial Laboratory) bearing spontaneous mammary carcinomas. In 30 per cent of the treated animals the tumors disappeared completely. Even when the animals were subjected to a careful post-mortem examination (many months after the complete disappearance of the tumors), no trace of malignant tumor cells could be found.

Every tumor animal is subjected to a biopsy before treatment is started. Thus there can be no question as to the correctness of the diagnosis.

Some of our critics raised the objection that the biopsy might be instrumental in healing these tumors. This objection seemed absolutely unfounded. Every clinician knows that biopsies never effect cures of tumors; if anything, they cause them to spread or grow more rapidly. However, in order to prove that the biopsy did not effect a cure, we subjected 81 tumor animals to a simple biopsy. None of these tumors disappeared.

These spontaneous tumors when subjected to treatment do not present the hemorrhages which were observed in transplanted tumors. They simply shrink gradually in size, undergo a drying-up process and disappear. Sometimes 8 to 10 daily intravenous injections will heal these tumors. In other instances (especially in large tumors) daily intravenous treatment may have to be extended up to six weeks. It is interesting to note that even a shrinking tumor will start to grow again, if the injections are interrupted.

The "healed splenic extract" as we have called it, for want of a better name, presents a new biologic principle, namely the use of an organ from an animal which had been cured of its cancer by treatment with spleen extract. Great as the scientific interest of this method might be, its practical application, for obvious reasons, would always be limited unless the active principle in these "healed" spleens could be freed and synthesized chemically, a research problem of great magnitude.

May I briefly interrupt this report on progress in order to discuss with you the significance of these experiments. You may know that Cancer Research in its present form dates back about forty years to the days of Paul Ehrlich. Since then innumerable efforts have been made all over the world in an attempt to cure spontaneous malignant tumors in animals by an indirect route (subcutaneous, intravenous or intraperitoneal application). Practically all of these experiments have failed. In recent years a few scattered reports of disappearance of these tumors in a few animals were presented. However, the high toxicity of the substances which were employed made their use on a large scale problematical, not to mention the impossibility of using them in patients.

Our work demonstrated for the first time that spontaneous malignant tumors in mice may heal completely in 30 per cent of the animals. These 30 per cent do not include the tumors which, though much reduced in size, do not disappear completely. If the latter were included, the figures would rise to 60 per cent.

As you know we have in recent years substituted yeast extract for spleen extract. Results with yeast extract have been practically identical with those obtained with spleen extract. At the International Cancer Congress in Atlantic City (1939) Maisin, who was then Director of the Cancer Institute in Louvain, Belgium, stated that by adding baker's yeast to the food of his animals he could retard the growth of experimental cancers.

A yeast extract was prepared in this laboratory about two years ago and injected intravenously into mice bearing spontaneous malignant breast tumors. Results obtained were practically identical with those following treatment with spleen extract. Again we noted complete disappearance of the tumors in 30 per cent of the treated animals.

I cannot dwell here on the many steps in purification and fractionation of the yeast extract. Details of this work have been presented in a number of papers published by our group. Progress has been made in two directions: 1) detoxication of the extract, 2) concentration of the tumor-active and removal of the tumor-promoting substances. The improved extract shows very little toxicity, whereas the original extract caused a temporary shock immediately following the injection.

We have observed many animals for more than one year after the complete disappearance of the breast carcinoma. Not only did the tumor fail to recur, but a complete pathological examination failed to show abnormalities in other organs.

However, I should point out that not all the animals remain free from recurrences. In about 25 per cent of the healed mice tumors recur usually after six to eight months. These tumors are resistant to treatment. Are they actually recurrent tumors or are they new tumors which may occur at any time in a cancer strain like Strain A?

Up to now we have not been able to increase the percentage of cures above 30 per cent. With the intensive work which is now going on in our chemical laboratory we should be able to raise this figure to at least 60 per cent.

Recently we published some very interesting results in prevention of tumor growth in a transplantable tumor which normally shows 95 to 100 per cent "takes." When these animals are treated with intravenous injections of yeast extract on ten consecutive days before the transplantation, the tumor will not "take" in 20 per cent. When pantothenic acid was mixed with the yeast extract, the "non-takes" rose to nearly 50 per cent. When yeast was mixed with riboflavin, the "non-takes" rose to above 60 per cent.

These observations which we presented in detail in *Science* indicate the vital role which the vitamins play in our problem. The scientific staff of Messrs. Merck & Company are now in active cooperation with us on this problem. As you know they are among the leaders in vitamin studies.

Among the many unsolved questions are the following: We have succeeded in curing spontaneous breast cancers in mice with two different extracts, one originating from the spleen, the other from yeast. What is the connecting link, what is the tumor-active principle inherent in both extracts? If we had the answer to this question, we would have taken a great step towards the solution of the problem.

How much have we accomplished? Possibly very little, possibly a

great deal. If our work has taken us near the end of our road, if we cannot apply our experiences and our results to the wider field of human pathology, this piece of research will have a limited application and will always remain of minor importance.

If we should be able—as we hope to try in the near future—to get results in cancer patients, our five years' efforts will bear fruit in a wide field.

It is the charm and the joy of research that the future of any research problem is full of hope and speculation.

In order to excuse their lack of endeavors in the line of research, doctors will often state that the field for research is too narrow now, as most problems in medicine have been solved. The contrary is the truth. Most problems in medicine—and for that matter in all the other fields of science—stay unsolved.

I hope that this contribution to your Anniversary Volume written mainly for intramural use—namely for the Journal of The Mount Sinai Hospital—will be read by the members of our intern staff. I trust that this brief description of the development of a new laboratory will induce these young men to develop their love and devotion to some research problem. They will be abundantly paid for such efforts by the joy of exploring new roads. Furthermore, I hope that they will have as much pleasure and satisfaction as our group has encountered in our research work during the last five years.

With my heartiest congratulations and best wishes,

Cordially yours,

October 1st, 1941.

Richard LewisoHN

NOTES ON CLINICAL OBSERVATIONS AND METHODS. II

EMANUEL LIBMAN, M.D.

[*New York City*]

A few years ago, in this Journal, I published an article with the same title.¹ It was my intention at that time to publish a series of such papers. On this occasion, I will add some further observations.

In the former paper, I referred to the subject of suppurative adenoiditis. The following is an additional observation.

It concerns a child, suffering for several weeks from an irregular fever. A few days before the onset of the fever, there had occurred a small injury to the skin about the nail of one of the fingers. This was followed by a local infection of moderate degree, unaccompanied by lymphangitis or cellulitis. This infection had subsided when I saw the child, leaving some redness and a little tenderness. Two blood cultures had revealed a small number of colonies of *Streptococcus hemolyticus*. There was no evidence of metastases, endocarditis or phlebitis. It was clear that the lesion of the finger was not maintaining the bacteremia. It was, therefore, necessary to look for another possible primary focus. Finding none in a careful examination of the body, I thought of infected adenoids as a possible source of the infection. A few moderately enlarged cervical lymph nodes could be palpated high up in the left side of the neck, near the mastoid bones. I succeeded in eliciting the fact that for a couple of days there had been a little bleeding from the left side of the nose. On palpation of the nasopharynx, a hard mass was detected filling the entire vault. This was broken up by the finger, the centre of the mass being softer. On the following day the fever had disappeared. A subsequent blood culture remained sterile. The child made a rapid recovery. The physician in charge reported to me later that the hard mass had disappeared, and that a moderate amount of adenoid tissue could be palpated.

This case illustrates the necessity of keeping adenoiditis in mind. It also teaches that every case of general bacterial infection needs careful study as regards the site of the primary focus and the location and significance of any metastases. Sometimes, as in this case, a consideration of the number of bacterial colonies plays a significant rôle in diagnosis and therapy. For example, in this case the number of colonies to the cubic centimeter was not over five. Such a number of bacteria could not of itself cause the fever and other general symptoms. It requires many bacteria in the blood to give a clinical picture. Most bacteremias of

¹ J. Mt. Sinai Hosp. 5: 197, (November-December) 1938.

streptococcic or staphylococcic origin are maintained by the primary focus (with or without venous involvement), an endocarditis or certain kinds of metastatic foci. Sometimes I refer to such calculations, in a general way, as "the mathematics of infections."

* * * *

In inspecting the throat particular attention should be paid to the margins and back of the uvula. A membranous inflammation of the nasopharynx may spread down the back of the uvula and extend forward only as far as the margins, the anterior surface remaining free. Such an appearance may be the only clue to the presence of agranulocytic angina.

* * * *

A physician who was working with the bacillus of diphtheria, complained for several days of fatigue, malaise and pain in the back of the neck, especially evenings. There were slight temperature elevations. There were a few enlarged lymph nodes at the angles of the jaws. Digital examination revealed a membrane in the nasopharynx, and cultures revealed virulent Klebs-Loeffler bacilli. Prompt recovery occurred on the administration of anti-toxic serum. This observation again emphasizes the importance of digital exploration and of inspection of the nasopharynx, especially in patients suffering from pain in the back of the neck. Diphtheria confined to the nasopharynx is easily overlooked.

* * * *

Although there have appeared, on occasion, papers on the subject, small lymph nodes, both in the lateral cervical region and directly supraclavicular are often overlooked. They are not as frequently tuberculous as generally believed.

I remember well a nonfebrile patient suffering from thrombocytopenic purpura, in whom the roentgenologist reported miliary tuberculosis of the lungs. This was at a time when it was not known that such a lesion could occur with little or no fever. On the side of the neck there could be palpated a node of little over millet size. On removal it revealed a fresh miliary tuberculosis. This helped to clear the case up, and demonstrated that tuberculosis can give rise to a hemorrhagic state characterized by the findings associated with thrombocytopenic purpura. Some may consider that the two disorders in the case here described may have been coincidental. But there is enough other evidence that tuberculosis can cause a bleeding state, accompanied or not by erythrocytosis.

Occasionally careful watching of a cervical node may aid much in diagnosis. In a patient in whom the diagnosis wavered between typhoid fever and the extension of a pulmonary tuberculosis, a node the size of a pea was palpated just above the clavicle. Because the node gradually enlarged, the diagnosis of tuberculosis was considered more likely. The subsequent course of the case proved the correctness of this assumption.

In searching for the so-called Virchow node, one must palpate not only near the inner end of the clavicle, but also the rest of the supraclavicular fossa. Not infrequently it is found at about the middle of the bone. It may be so jammed in this location that difficulty may be encountered in distinguishing it from a normal or an atypical bony structure. In cases of carcinoma of the stomach, it is practically always to be found on the left side. With other carcinomas (especially of lungs) it may be found on either side.

In the French literature this metastatic lesion is called the Troisier node. It has interested me to note that Rupert Willis, of Melbourne, refers to it by this name, in his remarkable volume, "The Spread of Tumors in the Human Body," published in London in 1934. I do not know the origin of this discrepancy. I am glad to add that I consider Willis' book one of the best on the subject of neoplasms, and that it should be in the library of all medical men.

* * * *

When a group of enlarged cervical or axillary lymph nodes is palpated, it may be of value to palpate carefully between the nodes and about them for strands (involved lymphatic channels). If such strands show fine beading it is very suspicious that the lymphatic disease is of tuberculous origin.

* * * *

It is important to note that nodes which are the seat of Hodgkin's disease may be but slightly enlarged. About twenty-two years ago, I was consulted, while on a holiday in Pennsylvania, by a man from New York City, who was suffering from a diffuse swelling of the sternum and two ribs on the left side. He was interested in having a diagnosis of syphilis excluded if possible. He knew that Hodgkin's disease was considered a fatal disorder, but said that he would rather have that or cancer than be "unclean." The general examination, apart from the osseous swelling, revealed a small group of enlarged nodes at the internal end of the right supraclavicular fossa. The largest was only of the size of a pea. When I examined the patient in the early morning I suspected tuberculosis because of the small size of these nodes. I was indisposed at the time and advised the patient not to return to New York until I examined him later in the day. In the afternoon, with a clearer head, I noted as he walked about the grounds of the hotel, that he had the peculiar ochre-yellow color which I associate with advanced Hodgkin's disease. I promptly sent for him and asked whether he had suffered from pruritus. He responded, "That is a remarkable question. I suffered from severe itching of the lower extremities for over a year before the swelling of the bones appeared. The doctors did not consider it of any significance, and did not bother about it." I then told him that I suspected the presence of Hodgkin's disease. He was jubilant because I did not speak of syphilis. One of the nodes and a biopsy

of the sternal swelling revealed typical Hodgkin's disease. Later he developed the large lymph nodes characteristic of the disease.

* * * *

The configuration of the enlarged lymph nodes of Hodgkin's disease may show certain characteristics. Often it can be noted that even when not pressed against each other, the nodes are almond-shaped, one margin being bevelled (or well rounded) and the other sharp. In a patient suffering from long-standing fever with slight splenic enlargement the only palpable node was found by rectal examination. It was close to the bony wall, and had been considered to be an osteoma. Because of its configuration I stated that its presence strengthened the diagnosis of Hodgkin's disease that had been ventured. The diagnosis was later confirmed by the development of packets of large lymph nodes elsewhere with the typical histological features.

Not infrequently the cut section of the nodes in Hodgkin's disease presents a peculiar ochre-yellow color. This color may become more intense by exposure to the air, and sometimes after preservation in formalin.

* * * *

In the condition which now is often referred to as Libman-Sacks' disease, involvement of lymph nodes plays a conspicuous rôle. Of 24 cases recently described by Dr. Tracy Mallory 20 showed such involvement.

Lymph node involvement had been known to occur in the disease. Usually reference was made to moderate enlargement of discrete cervical nodes, occasionally axillary or inguinal. Now we know that packets of enlarged nodes may be observed. They have been noted mainly in the supraclavicular region and the axilla. But they may be encountered in the mesenteric and retroperitoneal nodes. In one case, there was present a packet of nodes to the right and left of the trachea. Biopsies of enlarged nodes in the disease have been reported as hyperplasia, Hodgkin's disease (I know of two such cases) and giant follicular lymphoblastoma (one case). Careful histological examination may reveal the "hematoxylin-staining bodies" of Louis Gross or multiple small areas of necrosis.

The configuration of large nodes in the axilla and groin has been striking in a few cases. In one, those in the axilla were about the size of a large marble, and were in general, spherical with small irregularities. In another patient the nodes in the groin were peculiar (perhaps characteristic). They were broad nodes, larger than almonds, flat like lima beans.

In one case very large nodes in the axilla and groin disappeared many weeks before the patient passed away. This spontaneous disappearance is a novel observation. It goes hand in hand with other waves in the disease. For example, the lupus can disappear and return, and the endocarditis may heal and recur.

The presence of such enlarged nodes is of great aid in the recognition of

cases of Libman-Sacks' disease in which there is a complete absence of lupus erythematosus disseminatus, particularly when associated with arthritis (especially of the deforming kind), pericarditis, glomerulonephritis or combinations of these conditions.

* * * *

There has been confusion in relation to the designation "Oliver-Cardarelli's sign" for the tracheal tug. Oliver and Cardarelli did not describe exactly the same manoeuvre. Oliver described the tug as being revealed when the larynx was pushed upward, while Cardarelli referred to pushing the larynx to the left. My practice has been to push upward and if necessary to the left. There is no objection to the use of the term Oliver-Cardarelli sign, if all this is understood. The description of a separate "Cardarelli sign" for the tracheal tug might easily be misleading because that designation has been used for another sign described by Cardarelli (and also by Olshausen). This is defined as follows: "When a tumor is found in a young unmarried woman, lying anterior to the uterus, it is likely to be a dermoid cyst." I have no personal knowledge of the value of this diagnostic point.

* * * *

For many years I have found an aid in the diagnosis of mediastinal disease, especially neoplastic, in the presence of what I have designated *fixation of the larynx* (really fixation of the trachea). This is determined by attempting to push the larynx upward, by pushing upon the cricoid cartilage. Usually there is a good degree of mobility. When the sign is definite, the larynx cannot be budged. I do not lay stress on the absence of the sign except in young people with a long neck. In individuals with a short neck, I do not lay stress on the absence of the sign. In cases of aneurysm of the aorta, tracheal tug may be elicited at the same time as fixation.

As examples I will cite two cases, the first of which was observed before the advent of roentgenologic examination. The patient suffered from recurrent pleural effusion on one side of the chest. No diagnosis had been made before I found that laryngeal fixation was demonstrable. The patient proved to have a mediastinal neoplasm. The other patient was a child suffering from fever for many months, the cause of which could not be determined. The only physical sign that could be found was a fixed larynx. I ordered a roentgenologic examination, which was reported negative. Only an antero-posterior study had been made. I felt so sure that mediastinal disease was present that I insisted upon a lateral view. Then a mass was located in the posterior mediastinum, which eventually proved to consist of tuberculous lymph nodes.

NEPHROSIS AND THE "NEPHROTIC SYNDROME"

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There are many controversial problems in Bright's disease and their discussion goes back to the very days of Bright, who in his first publication (1827) anticipated the differentiation of the ailment into the triad of Volhard and Fahr, into nephritis, nephrosis and sclerosis.

As far as nephrosis is concerned we are confronted with the difficulty that this term has changed its meaning repeatedly. F. Mueller introduced this term in order to differentiate between inflammatory and degenerative processes. The matter became complicated when edema, albuminuria, hypoproteinemia and hypercholesteremia were designated the "nephrotic syndrome." This terminology is by no means justified. The syndrome is not found in all the nephroses and is present in many cases of chronic glomerulonephritis as well.

The most typical nephrosis in the sense of Mueller is the pathology in acute mercury poisoning. Here is the most severe degeneration of the renal epithelium, but the nephrotic syndrome is not present. In early stages of lipoidnephrosis this syndrome exists without any pathology in the kidney. There seems to be no doubt that degenerative tubular lesions and the nephrotic syndrome are independent of each other.

The features of the nephrotic syndrome are not inseparably linked. Taking the chief items, albuminuria, edema and hypoproteinemia into consideration, each of them may exist in the absence of the others.

Some light seems to be thrown upon the mechanism of the nephrotic syndrome by a peculiar condition known for more than 50 years, termed by its discoverer, E. Wagner, "edema of unknown origin" and now recognized by P. Jungmann as hypothalamic edema. The main features of this chronic ailment are chronic edema and marked hypoproteinemia in the absence of albuminuria and cardiac failure. A characteristic case of this kind may serve as an illustration:

A woman, 45 years of age, developed generalized edema 25 years ago during pregnancy. The edema persisted until death despite many therapeutic efforts. During many years of observation it was seen again and again that edema and body weight increased during the days preceding the menstrual period. There was neither nephritis nor cardiac failure. Anemia at times as severe as 4.8 gm. per cent hemoglobin and 2.4 million erythrocytes was a predominant feature. There was a marked leucopenia (2,000) and a persisting hypocalcemia (4.7), arterial hypotension and the

"hypothalamic blood sugar curve." Necropsy revealed a normal heart, normal vessels and tubular degeneration of a few small areas of the kidneys.

In a number of cases of this kind the central nervous origin of the edema can be seen by its unilateral appearance.

The case just mentioned with its beginning during pregnancy could be considered as being related to the nephrosis in toxemia of pregnancy. This particular nephrosis is not a renal disease as manifested by its prompt disappearance with delivery.

Hypoproteinemia has been observed in various hypothalamic-pituitary disorders. Inversed albumin-globulin ratio is a most common phenomenon, closely related to the process of infection, sensitization and immunization. A number of facts point to its autonomic nervous control.

Hypoproteinemia and hypercholesterolemia certainly are unrelated to albuminuria. In the case of a boy we have seen renal disease developing acutely with typical edema. At the very beginning of the ailment he showed hypoproteinemia and hypercholesterolemia. The urine, however, was free of albumin for the first few days.

Lipoidnephrosis is a systemic disease. The low basal metabolic rate found in a number of cases does not suggest hypothyroidism as has been assumed by Epstein. Increase as well as decrease of the basal metabolic rate may result from hypothalamic lesions and is then characterized by marked resistance to thyroid therapy. A low basal metabolic rate is also found in hypertensive glomerulonephritis when the nephrotic features are present. All cases of nephritis and nephrosis with low basal metabolic rates require extraordinarily large doses of thyroid, as large as 4 to 6 mg. daily without showing any discomfort or objective signs of intoxication.

From these facts and considerations the suggestion may be presented that Bright's disease has a twofold mechanism. One deals with the renal circulation, it leads to circulatory derangement in the territory of the kidneys and to arterial hypertension. The nature of this process deserves a special discussion. The second mechanism is systemic and not at all indispensable. It is represented by a hypothalamic disorder and involves a number of vegetative functions and regulations. Under the circumstances of infection, immunization and sensitization the hypothalamus always is affected. This is evidenced by pyrexia and other phenomena and in a particularly impressive manner by the miraculous curative effect of an intercurrent infection upon nephrosis.

The two mechanisms are independent of each other. Thus, we have chronic and even advanced glomerulonephritis without any nephrotic features and we have pure nephrosis without any glomerular involvement. Frequently both mechanisms are active. The initial glomerular process may recede and the nephrotic syndrome may remain and lead to a post-nephritic nephrosis.

INVOLVEMENT OF THE HEART IN SARCOIDOSIS OR BESNIER-BOECK-SCHAUMANN'S DISEASE

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It is now well recognized that sarcoidosis, benign lymphogranuloma, or Besnier-Boeck-Schaumann's disease, may affect any organ or tissue in the body and on this account it appears in a great variety of clinical forms. In the vast number of publications on the subject, much attention has been paid to the lesions in the skin and in the bones; to the changes in the lungs and lymph nodes; to the involvement of the structures of the eye and of various portions of the nervous system. On the other hand, only occasional references have been made to the important though somewhat less frequent effects which the disease produces upon the heart and the circulatory system. The paucity of autopsies upon cases of sarcoid may well have some bearing on this matter, but in 1935 Salvesen (1) first directed particular notice to this phase of the subject when he recorded the history of a patient with Boeck's sarcoid whose electrocardiograms showed bundle branch block alternating with a regular rhythm. The alterations in the electrocardiogram were interpreted as being caused by a nodule in the myocardium. Though there was no autopsy Salvesen attributed these effects to an invasion of the myocardium by sarcoid.

Since that time little attention has been paid to the interesting and serious effects which may arise from involvement of the heart and its surrounding structures. In the reviews by Pinner (2) and Snapper (3) the subject is scarcely mentioned; and Pautrier (4) in his large monograph on Boeck's Sarcoid does little more than allude to the occasional involvement of the heart. Palmer (5) in a recent review accords the subject a short paragraph; Schaumann (6) has pointed out that heart failure may occur as a complication in some patients.

When lesions have been found in the heart at post-mortem they have usually been recorded as curiosities, but an actual survey of the distribution of anatomical lesions, recorded at autopsies, shows, nevertheless, that the presence of sarcoids in the myocardium or pericardium is not very rare. This occurred in 4 of the 21 recorded autopsies which it has been possible to analyze (Bernstein, Konzelmann and Sidlick (7); Schaumann (6); Nicherson (8) and Cotter (9)). It is worthy of note that in at least three of these patients symptoms of myocardial failure were present during life. Schaumann (10), who in 1914 first emphasized the fact that Boeck's

sarcoid was a generalized disease, describes one case in which the heart during life was enlarged, and in which an electrocardiogram showed right sided preponderance and a second case in which extrasystoles were noted. In the first instance the heart was found to be enlarged at autopsy and sarcoids were discovered in the pericardium. In the second case the heart was normal at autopsy and free from sarcoids. One of Nickerson's six patients was dyspneic during life and was found to have an enlarged heart. At autopsy sarcoids were scattered through the myocardium and pericardium.

The fatal case reported by Cotter (9) is of especial interest. The patient was a colored boy of 18 whose chief symptoms were fatigue, cough, dyspnea, orthopnea and edema of the ankles. He showed an enlarged heart, with precordial bulge, and venous congestion. The second pulmonary sound was accentuated but there were no murmurs. The blood pressure was 140 systolic and 110 diastolic. There were râles over the bases of the lungs and slight anemia. The evidences of myocardial failure were progressive. Electrocardiograms showed at first sinus rhythm and tachycardia with arborization block. The arrhythmia changed later to auricular fibrillation, complete heart block and alternating pacemaker. At autopsy there was extensive infiltration of the myocardium and pericardium by sarcoid, accompanied by considerable fibrosis. Harrell (11) has recorded electrocardiograms from 8 of his 11 patients. Prominent P waves were present in 2 and flat or inverted T waves were found in 2. There were no symptoms or physical signs in these patients which would lead one to suppose that there were anatomical lesions of the heart or disturbance in its function. In the four remaining cases the electrocardiograms were normal.

A survey has recently been made of 31 cases of sarcoid or benign lymphogranulomatosis (Schaumann) which have been studied at the Johns Hopkins Hospital during the last 15 years (12). Six of these patients presented evidence during life of some derangement of the heart's action or showed at autopsy sarcoids in the myocardium or pericardium or in both situations. In one of these fatal cases which came to autopsy there were during life no symptoms or signs to suggest disease of the heart; and in this instance only scattered solitary sarcoids were found on microscopical examination of the myocardium. Of the remaining five patients, three died. Autopsy in two showed extensive involvement of the myocardium by sarcoids in one of these associated with dense scars. A detailed account of the pathological lesions found in these patients will be published by Dr. Vandergrift. In selecting these five cases for consideration several patients with more or less severe dyspnea have been excluded for in them the extent of disease of the lungs or mediastinum was sufficient to account for their symptoms. Though there may have been involvement of the heart and pericardium in addition there were no actual signs to indicate that this had occurred.

CASE REPORTS

Case 1. History (Adm. 111899). The first patient, a colored woman 28 years of age was admitted to the Johns Hopkins Hospital on July 27, 1937. She had had "mumps" as a child but otherwise had been well until about the first of June 1937 when she felt sluggish and began to lose weight. A scaling eruption appeared on the arms and legs, there was blurring of vision and redness of eyes. On June 24 she was found to have a conjunctivitis with pericorneal injection. A few days later she became hoarse, coughed, noticed a lump in the throat, had difficulty in swallowing and regurgitated fluids through the nose. On June 28 paralysis of the right vocal cord was observed. On July 1 the liver and spleen were found to be enlarged, and the teleroentgenogram made on July 2 showed bilateral enlargement of bronchial lymph nodes with diffuse infiltration throughout the lungs. The heart, itself, was not enlarged, the shadow measuring 10.5 cm. in transverse diameter (fig. 1). On July 16



FIG. 1



FIG. 2

FIG. 1. Case 1. Teleroentgenogram of chest made on July 2, 1937, showing enlargement of peribronchial lymph nodes and diffuse filmy infiltration of lungs without enlargement of heart.

FIG. 2. Case 1. Teleroentgenogram April 11, 1940 showing decrease in size of peribronchial lymph nodes, some filmy infiltration of lungs, noticeable increase in size of heart.

there was a positive reaction to 0.1 mg. of old tuberculin. By July 22 she was unable to swallow liquids without regurgitation and an examination showed weakness of the soft palate, of the left pharyngeal muscles and left vocal cord.

Examination. On admission to the hospital she was found to have a mild irregular fever, slightly scaly somewhat elevated eruption over the legs, enlargement of the axillary lymph nodes, conjunctivitis and episcleritis, paralysis of the palate and of the left vocal cord with weakness of the sterno-mastoid and lower two-thirds of the trapezius muscles on the left, and enlargement of the liver and spleen. The heart was not enlarged, the dullness reached 8 cm. to the left in the fifth space and 2.5 cm. to the right in the fourth space. There were no murmurs or accentuations. Pulse rate, 100 per minute. Blood pressure was 120 systolic and 70 diastolic. An electro-

cardiogram made on July 2 showed a P-R interval of 0.16 seconds; the QRS duration normal; normal sinus rhythm; T₁ and T₂ upright, T₃ inverted; ventricular extrasystoles and levogram. A teleroentgenogram made on July 28 showed much the same condition as on July 2. The red blood cells were 5,200,000; hemoglobin 110 per cent, sedimentation rate 18 millimeters, leucocytes 5,500, polymorphonuclear neutrophils 66 per cent, eosinophiles 4 per cent, lymphocytes 24 per cent, monocytes 6 per cent. The Wassermann reaction was negative, the non-protein nitrogen of the blood 30 mg. per cent and the plasma proteins 6.01 grams per cent.

Course. The fever continued and by August 2 the left arm was weak and the reflexes diminished. On August 2 the bromsulphalein test showed 25 per cent retention. On August 7 a tender nodule appeared in the left parotid gland. By August 21 there was improvement of the various pareses. By September 8 the temperature was normal. An electrocardiogram made on September 9, when digitalis had not been administered, showed practically the same changes as on July 2. On September 10 on microscopic examination the lesions of the skin showed the typical changes of sarcoid. By September 16 she was much better, the sedimentation rate had fallen to 7 mm., the leucocytic count was 6,000 with polymorphonuclear neutrophils 58 per cent, eosinophiles 13 per cent, lymphocytes 23 per cent, monocytes 6 per cent. On September 18 the total plasma proteins were 6.3 grams per cent and the albumin-globulin ratio was 58/42. She continued to improve and she was discharged from the hospital on October 18, 1937.

Follow-up Course. She was not seen again until April 1940. On April 25, 1940 she seemed well but complained of slight shortness of breath. The heart was somewhat enlarged. There was a loud systolic murmur at the cardiac apex with occasional extrasystoles. A teleroentgenogram made on April 11, 1940 (fig. 2) showed an increase in the size of the heart above that noted three years previously, the transverse diameter now being 13 cm. The shadows at the hila were not so dense but there was some infiltration of the lower right lung. The electrocardiograms now showed P-R interval of 0.16 seconds; QRS of normal duration, rate 103; sino-auricular rhythm; T₁ and T₂ higher than before; T₃ has become isoelectric; T₄ is upright. The electrical axis has shifted from levogram to normal. The liver and spleen were not palpable. The blood proteins were 7.62 grams per cent, the albumin-globulin ratio was 40/60.

During the acute attack of uveoparotid fever with widely disseminated sarcoidosis it is likely that the heart of this patient may have become involved in the process. Following the attack the heart enlarged and three years later there was evidence of slight myocardial insufficiency.

Case 2. History (Adm. 155971). The second patient was a colored man 29 years of age who was admitted to the Johns Hopkins Hospital on December 14, 1938 complaining of weakness, dizzy spells and pain in his joints. The family history was unimportant. In recent years his health had been poor. He had had occasional attacks of tonsillitis but no evidence of rheumatic fever. He had contracted gonorrhea in 1929. In 1932 he was seen in the out-patient department complaining of shortness of breath and difficulty in vision. He was found to have acute bilateral uveitis and by x-ray examination an irregular well outlined mass was seen in the superior mediastinum without enlargement of the heart shadow. It measured 11.75 cm. in total width (fig. 3).

He gradually improved but in 1937 experienced weakness and dizzy spells and it was found in November that though the mediastinal mass was smaller the bronchial nodes were still enlarged (fig. 4). The weakness increased in severity and later he developed pain in his joints.

Examination. On admission to the hospital he was found to be tall, fairly well

nourished with a high pitched voice and feminine configuration of the body. The fingers were long; there was slight generalized edema of subcutaneous tissue, and synechiae about the left iris with scars in the retina. The left axillary lymph nodes were enlarged. The lungs were clear to percussion and auscultation. The cardiac impulse was diffuse 9.5 cm. to left in fourth space. The heart was enlarged, the dullness extending 10 cm. to left in fifth space and 5 cm. to right in fourth space. The heart sounds were loud, the second pulmonic split and there were numerous extrasystoles. There were no murmurs. The blood pressure was 110 to 125 systolic and 80 diastolic. A teleroentgenogram made on December 20, 1938 showed a shadow in the superior mediastinum smaller than that previously observed, but a noticeable increase in the size of the heart shadow which measured 15.5 cm. in total width (fig. 5). An electrocardiogram made on December 17, 1938, when he had not had digitalis, showed a P-R interval of 0.26 seconds and a QRS interval of 0.11 seconds with bundle



FIG. 3



FIG. 4

FIG. 3. Case 2. Teleroentgenogram showing large irregular shadow in superior mediastinum without enlargement of the heart, made in 1932.

FIG. 4. Case 2. Teleroentgenogram showing decrease in mass in mediastinum with enlargement of heart, made on November 28, 1937.

branch block. On December 28 the QRS interval was 0.12 and the characteristic changes of bundle branch block persisted. The abdomen was protuberant, the liver was felt below the costal margin, the spleen was not palpable. There was little hair on body, the crines pubis of feminine type. The prostate could not be felt. The vibratory sense was diminished in the legs and arms.

The tuberculin reaction was negative to 10.0 mg. of old tuberculin. The Wassermann reaction was negative. The leucocytes were 4,100, with polymorphonuclear neutrophils, 49 per cent; eosinophiles, 9 per cent; lymphocytes, 34 per cent; monocytes, 7 per cent. The total plasma proteins were 8.5 grams per cent; albumin-globulin ratio 46:54. The blood calcium was 10.5 mg. per cent; the phosphorous 4.4 mg. per cent. The venous pressure was 70 to 80 mm. of water. An axillary lymph node was removed which proved to show changes typical of sarcoid. On July 9, 1939 an electrocardiogram showed a condition similar to that on December 17 (fig. 6).

Course. He left the hospital slightly improved but returned on February 24, 1939 complaining of dizzy spells, headache and mental confusion. The temperature was



FIG. 5

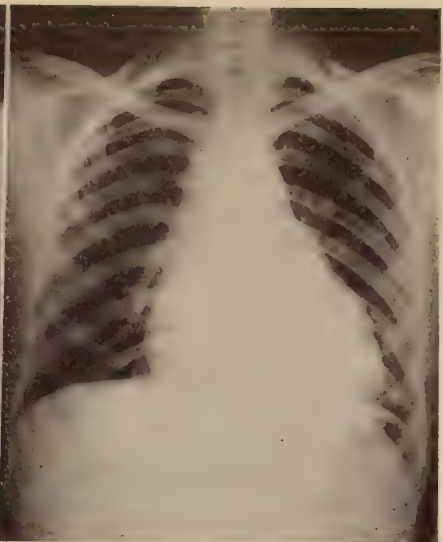


FIG. 7

FIG. 5. Case 2. Teleroentgenogram made December 20, 1938 showing still further increase in size of the heart.

FIG. 7. Case 2. Teleroentgenogram made on May 29, 1939 showing still further enlargement of the heart.

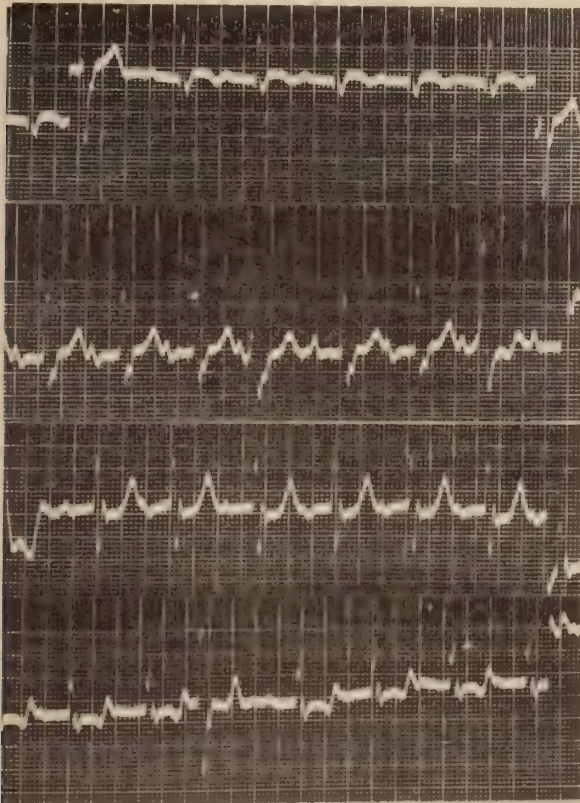


FIG. 6. Case 2. Electrocardiogram made on January 9, 1939 showing prolongation of P-R interval, bundle branch block and extrasystoles.

100.4°F. There was little change in his general condition. There was slight cyanosis but no edema. The heart attracted particular attention on account of its enlargement without murmurs but with loud second sounds at the base. The point of maximum impulse was in the fourth space 9 cm. to the left of midline. The dullness reached 10.5 cm. to the left in the fifth space and 5 cm. to right in fourth space. The blood pressure was 130 systolic and 70 diastolic. The liver and spleen were not felt. There was pitting edema over the shins. A teleroentgenogram made on February 29 and again on May 29 (fig. 7) showed persistent enlargement of the heart shadow which measured 15.25 cm. in total width. An electrocardiogram made on March 6, 1939, when he had not had digitalis, showed a rate of 100; P-R interval 0.28 second;

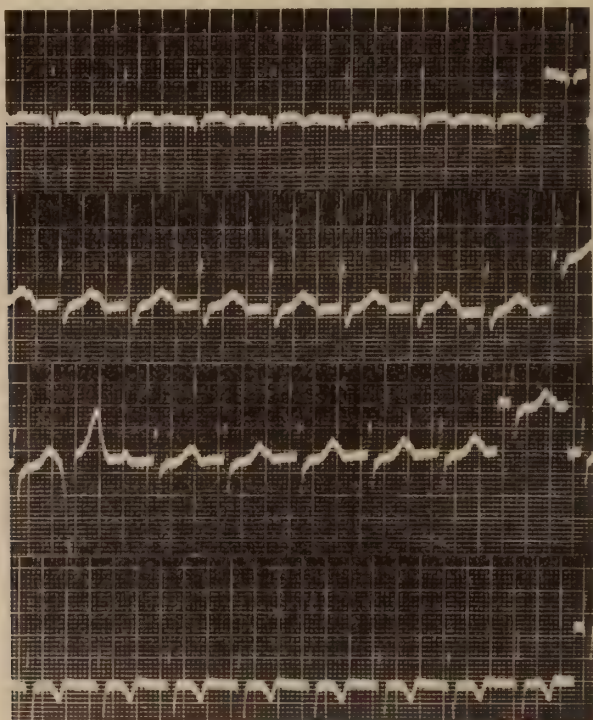


FIG. 8, Case 2. Electrocardiogram made March 6, 1939 showing much prolongation of P-R interval, bundle branch block and extrasystoles. Note changes in T waves from Fig. 6.

QRS duration 0.12 second; "T₁ slightly inverted; T₂ and T₃ upright; T wave in chest lead inverted and one premature contraction. There have been some changes in the T waves since the last record, indicating myocardial damage with changing condition" (fig. 8). He remained in the hospital until March 6 during which time he had slight fever varying from 99 to 100.2°F, but since his condition did not alter materially he was discharged on March 6 and observed in the out-patient department. He was last seen on September 12, 1939 when there was little change in his symptoms, physical condition or x-ray. He died in December 1939.

Comment. It is difficult to explain the cardiac abnormalities in this patient unless one assumes that the heart was involved in some manner by the lymphogranulomatous process. The persistent bundle branch block and progressive enlargement of

the heart without evidence of disease of the valves and in the absence of arteriosclerosis, nephritis, or syphilis lead to the conclusion that the damage was produced by sarcoidosis of the myocardium or pericardium or both.

Case 3. History (Adm. 200678). The third patient was a colored boy 20 years of age who was admitted to the Johns Hopkins Hospital on June 2, 1940. Early in May 1940 he had been attacked suddenly with abdominal pain and nausea. Later he started to cough, became progressively short of breath and his feet swelled.

Examination. He was admitted to the hospital in desperate straits, with a temperature of 101°F., extreme dyspnea, orthopnea, cyanosis, tachycardia and extensive edema. There was some enlargement of all the superficial lymph nodes and engorgement of the veins of the neck. The venous pressure was 370 mm. of saline. The anasarca shifted to some extent and was most prominent on the right side. There

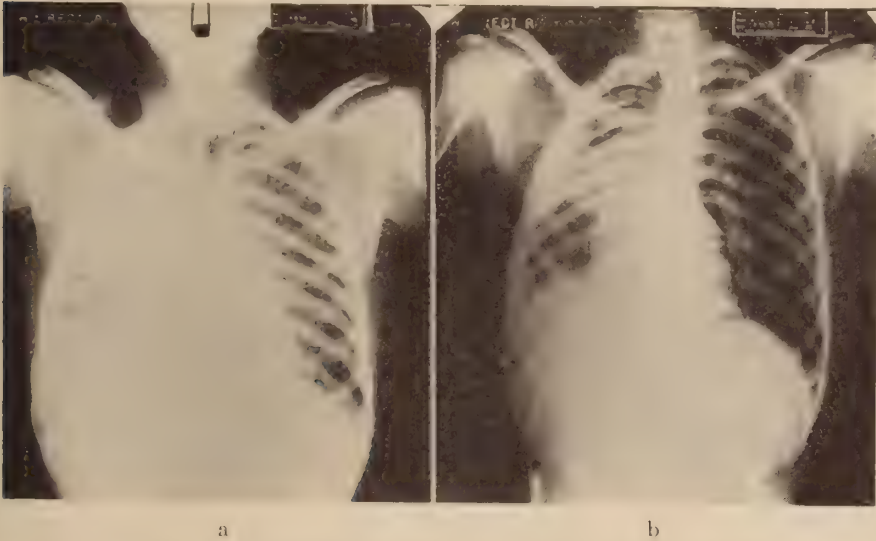


FIG. 9a. Case 3. Teleroentgenogram made on May 8, 1940. Extensive clouding of right lung and miliary mottling of left.

FIG. 9b. Case 3. Teleroentgenogram made on May 14, 1941 showing persistence of small shadow in right lung, clearing of left lung and displacement of the heart to the right.

were signs of partial consolidation of the upper portion of left lung, with râles throughout both lungs and evidences of fluid in the right chest. The heart was not obviously enlarged, the dullness extending 7 cm. to the left in the fifth space. The sounds were loud with a blowing systolic murmur over the precordium. The blood pressure was 120 systolic and 60 diastolic. An x-ray made on May 8 showed a dense shadow in the upper right chest with clouding of the lower right and shadows at the left root (fig. 9 a). There was cough with some bloody expectoration. The abdomen was distended, the liver protuberant and greatly enlarged, the spleen readily palpable and firm. The lower extremities and right side of body were much swollen. The hemoglobin was 105 per cent; the red blood cells 5,300,000; leucocytes 6,300, with polymorphonuclear neutrophils, 81 per cent; lymphocytes, 18 per cent; monocytes, 1 per cent. The sedimentation rate was 26 mm. The urine on admission showed albumin 3 plus with occasional leucocytes and casts. An x-ray examination of the chest made in May showed a shadow in the upper right chest with innumerable

miliary shadows in the left lung. An x-ray made in June showed dense clouding of the entire right chest with shadows at the left root. The non-protein nitrogen of the blood was 40 mg. per cent, the total plasma proteins 6.35 grams per cent.

Course. It was evident that he was suffering from severe cardiac insufficiency, combined with an extensive pathological process in the right lung. On June 4, 30 cc. of straw colored fluid was removed from the right chest. He became more dyspneic and was, therefore, placed in an oxygen tent and given digitalis. An electrocardiogram made on June 15, 1940, after he had had digitalis for 8 days, showed a sinus tachycardia; P-R interval of 0.17 seconds; an inversion of T wave in the first lead; a diphasic T wave in the second lead; an upright T wave in the third lead; and an inverted T wave in the fifth lead. In view of the fact that the patient had received digitalis the interpretation of these changes was not entirely clear, but they were read as indicating some myocardial damage. The tuberculin reaction was negative to 0.01 mg. and 1 mg. of old tuberculin. The sputum showed no tubercle bacilli.

There was a gradual improvement but on June 18 he was still cyanotic and the venous pressure was 268 mm. of water. By June 22 the edema had disappeared and albumin was no longer present in the urine. There were numerous râles over the chest, there was a systolic murmur over the entire precordium and the second pulmonary sound was loud. By June 25 the liver could still be readily felt and the spleen was palpable and firm. One of the enlarged lymph nodes was removed for histological examination. It showed typical sarcoid in both the fresh and the healing stages. An x-ray examination of the hands showed a few small areas of decalcification in the phalanges.

There was progressive improvement and the patient left the hospital in comparative comfort on August 12, 1940.

Follow-up Course. During the autumn and winter of 1940 and 1941 he remained in fair health, doing light work without noticeable dyspnea, and gaining some weight. On May 14, 1941 he stated that he was working and felt well. He was still thin and underdeveloped. There was no dyspnea or cyanosis. There was a flat oval, slightly raised scaly eruption over the forearms which had appeared during the spring. The lymph nodes in the axillae were enlarged. The trachea was deviated to the right. The upper right chest was flattened and over this region both anteriorly and posteriorly the percussion note was extremely dull, the breath sounds tubular and accompanied by a few fine râles. There was dullness at the right base with some suppression of breath and voice sounds. The cardiac impulse was felt in fifth space 6 cm. from midline. The area of cardiac dullness was not increased measuring 7 cm. to the left in the sixth space; the border on the right was obscured by the dullness over the lung. The sounds were clear. There was no engorgement of the cervical veins. The tele-roentgenogram made on May 14, 1941 showed dense clouding over the right upper chest. The mediastinum was displaced to the right (fig. 9 b).

The liver was not definitely palpable but the firm rounded margin of the spleen protruded from beneath the costal margin. There was no edema. The examination of the blood showed hemoglobin 12.4 grams (85 per cent); red blood cells 4,740,000; leucocytes 5,500; polymorphonuclear neutrophils, 79 per cent; lymphocytes, 17 per cent; monocytes, 3 per cent; eosinophiles, 1 per cent; sedimentation rate, 22 mm. Tuberculin reaction negative to 0.01 mg. to 1.0 mg. and to 10.0 mg. of old tuberculin. The total plasma proteins were 8.20 grams per cent; the albumin-globulin ratio was 47/53; the blood calcium 9.5 mg. per cent, the phosphorous 4.4 mg. per cent.

He had continued to take with some regularity 0.1 gram of powdered digitalis daily. The electrocardiogram showed a P-R interval of 0.24 seconds; the QRS duration was normal; there was normal sinus rhythm and normal axis deviation; T₁ and T₂ were upright; T₃ was diphasic; T₄ was slightly inverted; and S-T₄ was elevated. There was first degree heart block and evidences of myocardial damage not accounted for by digitalis.

Comment. It is obvious, in this patient, that the right lung and mediastinum were and still are extensively involved in the process. It seems highly improbable, however, that the pulmonary lesion could of itself be entirely responsible for the symptoms and signs of myocardial failure which formed such a prominent feature of the acute illness. It is reasonable, therefore, to suppose that the myocardium, and possibly the pericardium, were also invaded by sarcoid. The result was serious interference with the heart's action.

Case 4. History (Adm. 217982). The fourth patient was a colored man 42 years of age who entered the Johns Hopkins Hospital on January 8, 1940 complaining of attacks of dizziness and fainting accompanied by pain over the heart. He had been seen at intervals in the out-patient department for ten years, for in 1932 he was found to have attacks of Adams-Stokes syndrome with some enlargement of the heart, an



FIG. 10



FIG. 11

FIG. 10. Case 4. Teleroentgenogram made on April 15, 1933 showing heart of comparatively normal size.

FIG. 11. Case 4. Teleroentgenogram made on January 9, 1941 showing great enlargement of the heart and shadows at roots of lungs.

inconstant diastolic murmur along the left border of the sternum, slow pulse and complete auricular-ventricular dissociation in the electrocardiogram. The Wassermann reaction was positive. He was treated intensively for syphilis. On April 15, 1933 a teleroentgenogram showed the heart shadow to be 12.25 cm. in transverse diameter (fig. 10). He gradually improved and had been free from his attacks of giddiness and syncope for about seven years when three weeks before admission the attacks of giddiness and syncope returned and were accompanied by pains over the heart.

Examination. He was a well developed man, the temperature was not elevated, and he did not appear ill. There was slight enlargement of some of the superficial lymph nodes. There was no dyspnea, cyanosis or edema. The lungs were clear to percussion and auscultation. The heart was much enlarged extending in the teleroentgenogram 11.0 cm. to the left and 6.5 cm. to the right, a total diameter of 17.5 cm. (fig. 11). The cardiac impulse was forceful and felt in the fifth space 9 cm. to the

left of the midline. The rate was slow averaging 40 beats per minute. At times extrasystoles were audible. There was a systolic and diastolic murmur along the left border of the sternum. The blood pressure was 130 systolic and 80 diastolic. The abdomen was soft. The liver was readily palpable, the spleen could be felt well below the costal margin. The blood count showed hemoglobin, 15 grams (105 per cent); red blood cells, 5,360,000; leucocytes, 7,200; polymorphonuclear neutrophils, 74 per cent; eosinophiles, 2 per cent; lymphocytes, 21 per cent; monocytes, 3 per cent; sedimentation, rate 8 mm. The urine showed no abnormalities. The Wassermann reaction was positive in spite of antisyphilitic treatment from 1930 to 1933. Electrocardiograms were made on several occasions and each showed complete auricular-ventricular dissociation with ventricular extrasystoles (fig. 12). The blood non-protein nitrogen was 30 mg. per cent. The total proteins 6.44 mg. The albumin-globulin ratio was 54/46. The Van den Bergh was delayed biphasic and the bilirubin was 2.3 mg. per cent; the cholesterol was 244 mg. per cent; the phosphatase activity was 12.3 units. There was 30 per cent retention of bromsulphalein. There was constantly slight fever varying from 99 to 100.8°F. by rectum and occasionally reaching 101°F. The electrocardiograms were as follows:

DATE	RATE	VEN- TRICLE	AURI- CLE	QRS	T ₁	T ₂	T ₃	S-T & F	II
1/ 9/41		44	107	0.12	Inverted	Isoelec- tric	Upright	Elevated	Depressed
1/11/41		37	101	0.12	Inverted	Biphasic	Upright	Elevated	Depressed
1/14/41		30	83	0.13	Inverted	Biphasic	Upright	Elevated	Depressed
1/21/41		32	100	0.12	Less in- verted	Upright	More deep- ly in- verted		
1/29/41		45	107	0.10	Inverted	Upright	More deep- ly in- verted		Depressed

Course. The patient was considered to have syphilitic aortitis with syphilis of the heart, complete heart block due probably to an old gumma, and cirrhosis of the liver. Under observation there were no attacks of Adams-Stokes syndrome. He became mentally deranged and committed suicide. An autopsy, performed by Dr. Gregory, showed that the aorta was delicate and free from any evidence of syphilis. The aortic valves were normal. There was a dense scar in the interventricular septum and microscopically fresh and old sarcoids were scattered through the myocardium, pericardium, pleura, lungs, spleen, liver and kidneys.

Comment. It would be impossible to exclude syphilis as a cause of the area of fibrosis which evidently involved the bundle of His and thus gave rise to the auricular-ventricular dissociation, but it can only be said that there were no lesions found that could be ascribed to syphilis and that the only abnormality discovered was the widely disseminated sarcoidosis.

Case 5. The fifth and last patient, a colored man 40 years of age, was not seen during life for he dropped dead on his doorstep when he was supposed to be in good health. The autopsy was performed by Dr. Vandergrift, who found marked enlargement of the superficial, mediastinal, mesenteric and retroperitoneal lymph nodes, large masses about the great vessels of the thorax with extensive infiltration of the

pericardium and myocardium by similar masses and nodules in the skin of the penis. Microscopically the tissue was found to be composed of sarcoids which in addition were disseminated through the lungs, liver, kidneys, spermatic cords and cerebral dura.

In the remainder of our patients an examination of the cardiovascular system has not shown any abnormalities and electrocardiograms from five of these presented no remarkable deviation from the normal, though in one there was slight elevation of the RST segment in leads II and III. The T waves were upright in all leads; the P-R

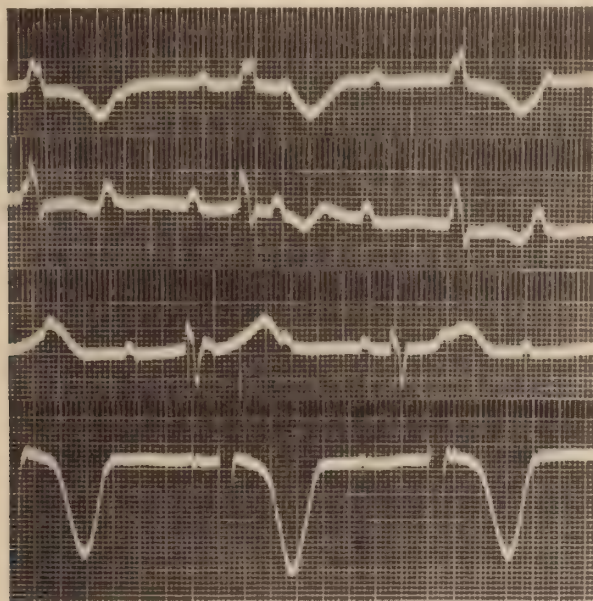


FIG. 12. Case 4. Electrocardiograms made January 11, 1941 showing complete auricular-ventricular dissociation with prolongation of QRS interval.

interval was 0.19 second and the QRS normal. The electrocardiogram showed low resistance.

DISCUSSION

From our own experience and from that of others it is evident that benign lymphogranuloma or sarcoid may invade both the myocardium and the pericardium. This has been observed in seven instances at autopsy so that it is not an extremely unusual occurrence. The recognition of this condition during life may in some cases be impossible for at times the lesions in the myocardium are scarce and widely scattered so that they do not interfere with the function of the heart. When, however, the nodules are collected in large groups or when they occur in particular situations they may give rise to a variety of signs and result in serious interference with the function of the heart. Enlargement of the heart appears to be common and occurred in four of our patients. It is noteworthy that the enlargement may not be accompanied by murmurs.

Different forms of arrhythmia with abnormalities in the electrocardiogram seem to be common. These may be transient, as noted by Salvesen, or may change from one type to another as was the case in the patient reported by Cotter. Persistent alterations in the T waves occurred in one of our patients. Arborization block has been noted and was present in one of the patients in this series. Complete and permanent auricular-ventricular dissociation indicates a lesion in the bundle of His (Case 4 of our series). With extensive invasion of the myocardium, such as occurred in Case 5, there may be sudden death. The electrocardiographic abnormalities observed in this series of cases are listed in Table I.

In certain respects the condition may resemble some instances of tuberculous pericarditis for there is often fever and there may be disease of the lung. Tuberculous pericarditis was considered as a possible cause of cardiac disease in both Case 2 and Case 3. The demonstration of sarcoid in the lymph nodes in both instances, lesions in the phalangeal bones in Case 3, and persistently negative tuberculin reaction in both patients

TABLE I
Cardiac abnormalities observed in six cases of sarcoid

	NO.	AUTOPSY
Enlargement of heart.....	5	2
Extrasystoles.....	1	
Abnormalities of T waves with myocardial failure.....	1	
Bundle branch block.....	1	Fatal—no autopsy
Complete heart block.....	1	Fatal—autopsy
Sarcoid in myocardium.....	3	3

appear to exclude the possibility of tuberculous pericarditis either as a primary disease or as a complication of benign lymphogranulomatosis.

Myocardial failure of various degrees of severity may occur. This may be progressive or, in other instances, even when the symptoms of failure are extremely severe, marked improvement may take place as happened in Case 3.

Though the symptoms and signs attending the invasion of the pericardium and myocardium by sarcoid are varied and irregular one might be led to suspect that the condition was present in a patient known to have sarcoidosis who presented evidence of an unexplained enlargement of the heart particularly when there were no murmurs, when there was no hypertension, when the tuberculin reaction was negative, or when an arrhythmia was present with abnormalities in the electrocardiogram indicating damage to the myocardium.

Though involvement of the pericardium and myocardium produces a serious situation which may lead to a fatal termination, it is possible

in some instances that the lesions may heal, and if they do not affect important pathways in the heart muscle improvement may ensue.

SUMMARY

In a series of 31 cases of sarcoidosis six patients showed some evidence of myocardial insufficiency during life or sarcoids of the heart and pericardium were discovered at autopsy. In one patient who showed no abnormalities of the heart during life a few lesions were found scattered through the myocardium at autopsy. The remaining five patients presented some evidence of disease of the heart. Three of these patients died. Autopsies performed on two of these cases showed sarcoidosis of the myocardium and pericardium.

The five patients suffered from various degrees of heart failure, often with enlargement of the heart, arrhythmias and electrocardiographic changes.

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ADAMANTINOMA OF THE HYPOPHYSEAL DUCT

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The literature on the various tumors which arise from the so-called craniopharyngeal duct, or hypophyseal duct, is very extensive and satisfactory, but still it is interesting to draw attention to the details of one type at a time, since when a large material is available certain forms, sharply separated and with characteristic structure, can be recognized. The present brief paper is stirred by the recent occurrence of a typical adamantinoma, or ameloblastoma, which presents the characters widely recognized and described by many authors, and exactly similar to those of fourteen other cases which have occurred in our material.

CASE REPORT

History. A man 46 years old, married for 20 years, without children. No illness except typhoid fever at the age of 14. For two or three years he had increasing drowsiness, forgetfulness and weakness in the legs and feet. Later he experienced the onset of violent attacks of vomiting and severe headache. There had been no polyuria. There had been complete impotence for several years and the general habitus was that of Fröhlich's syndrome. No physical signs nor neurological disturbances could be recognized. Operative search for a tumor in the cerebrum was futile and death occurred on the same day.

Necropsy findings (No. 17551). A supra-sellar tumor was present which pressed up into the floor of the third ventricle, a firm white mass measuring 3 x 2 x 2 cm., which pressed on the optic chiasm in its mid-portion was also present, but the optic nerves were not greatly involved. It projected fairly far to the left and overlaid the pons where it had a rounded lower surface. In the middle of the convex surface there was recognised the stalk of the hypophysis which was cut through at autopsy, and a projection of the tumor into the substance of the hypophysis followed the stalk, pushing it to one side (fig. 1). Upward the tumor extended into the third ventricle, interrupting the fornix and encroaching somewhat on the internal capsule on both sides, but not interrupting it. There was some compression of the corpus striatum on each side. The foramina of Monro were obliterated and the lateral ventricles contained a gelatinous material. The general situation is shown in figure 2. The other organs showed practically nothing abnormal.

Sections from this tumor show the characteristics which have been so well described in the papers of Erdheim (6), Peet (13), Critchley and Ironside (3), Frazier and Alpers (7), Duffy (5), Drummond (4), Strada (14), Husten (9), Love (11), Costero and Berdet (2), Harbitz (8), Krompecher (10), and others.

Microscopic description. Essentially this structure is as follows. The tumor has a loose, vascular stroma of connective tissue which surrounds and penetrates it, giving it in this case a smooth surface and an adequate blood supply. The masses of

epithelial cells have as a boundary a single layer of cylindrical cells in a palisade arrangement which is so typical of the enamel organ and has contributed the name ameloblastoma, or adamantinoma (figs. 3, 4, and 5). Beneath this is a second layer,

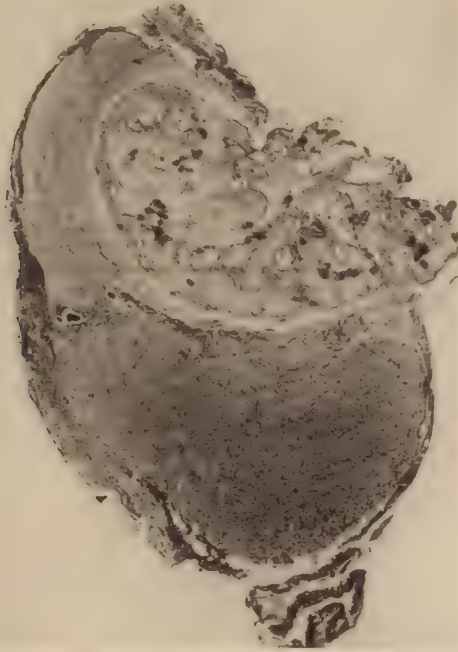


FIG. 1. Autopsy No. 17551. Compression of hypophysis and stalk by the tumor

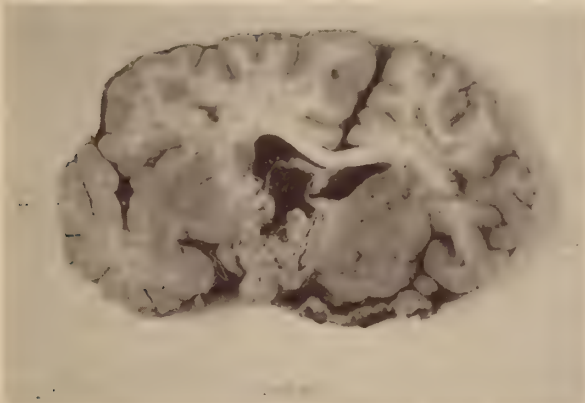


FIG. 2. Autopsy No. 17551. Extension of tumor into the third ventricle of the brain

much less distinctly developed, of smaller closely packed epithelial cells of indefinite form and this again resembles the arrangement in the enamel organ, the stratum intermedium, after which one passes inward into the stellate reticulum which forms



FIG. 3

FIG. 4

FIG. 5

FIG. 3. Autopsy No. 17551. Marginal portion of tumor with surrounding stroma

FIG. 4. Autopsy No. 13666. Typical portion of adamantinoma with palisade cells, stellate reticulum and squamous epithelium.

FIG. 5. Autopsy No. 10288. Typical portion of adamantinoma

the main mass of the lobule which is outlined by the enamel epithelium or ameloblasts. This stellate reticulum is made up of delicately branched cells, spread apart so as to form a loose network. In the interior of this mass there are, in nearly every lobule, round, concentrically laminated masses composed of larger distinctly squamous epithelial cells which have rather large nuclei and very definite keratohyalin granules in their cytoplasm (figs. 4 and 5). Many of these are well preserved, but others are partly calcified, or more completely calcified, and reduced to a formless mass of deeply staining calcified material (fig. 6B). Then the area appears disintegrated in the section on account of the many resistant calcified granules. Some areas of the stellate reticulum (of which, it must be remembered, that in spite of this

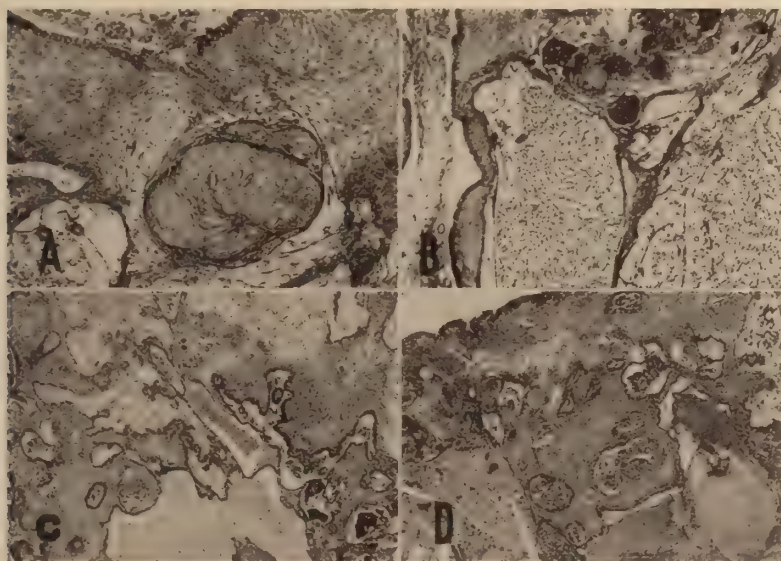


FIG. 6. Autopsy No. 17551. A) Squamous cell nodule with keratinization granules within stellate reticulum. B) Lobules of tumor with palisade cells, stellate reticulum and squamous cell nodules much calcified, spaces in stroma with colloid droplets. C) Tumor strand showing palisade epithelium, stellate reticulum, squamous epithelial masses with calcification, and cavities lined by connective tissue and containing colloid droplets. D) Lower power of tumor showing cholesterol crystals in one space.

nomenclature it is composed of epithelium) show large spaces with very thin, formless lining and containing what in some cases appears to be blood, but in other such large spaces a large number of minute bodies not exactly resembling red corpuscles and associated with tiny granules which appear to form short threads in places (figs. 6 C, D). These cavities, however, may be traced to the connective tissue stroma, the thin lining membrane in places showing elongated flattened cell nuclei. In some cases there are also blood-filled capillaries and more of the loose stroma although it is very difficult to trace the point of entry of such mesoblastic portions since they seem to be generally surrounded by the epithelial masses (fig. 6 B, C). Another characteristic is the presence of cavities in the epithelial structures in which among the cells there are abundant crystals of cholesterol which glisten when the fresh tumor is cut through (fig. 6D).

DISCUSSION

The material in the records of the Johns Hopkins Hospital contains 113 cases of tumor of the craniopharyngeal duct arising from the cells which later form the pars intermedia of the hypophysis and the pars tuberalis, and among them we have found 12 cases of the adamantinoma in addition to the three described by Duffy (5). The others, much exceeding these in number, must be studied separately.

The twelve cases, of which that already described was one, were very briefly as follows:

Autopsy No. 8163: Negro female, 42 years, very obese, vision hazy. Occipital headache. Edema and hemorrhage in retina. Tumor invading third ventricle, cystic and filled with crystals. Typical structure of adamantinoma, calcified in places.

Autopsy No. 10288: White male, 28 years. Visual disturbance and headache for a year. No vomiting. Blind on left. Hemianopsia on right. Typical adamantinoma extending into third ventricle. Left optic nerve invaded (fig. 5).

Autopsy No. 10499: Female, 18 years. Headache and loss of vision; bilateral choked discs. Typical adamantinoma with pressure on optic chiasm and invasion of third ventricle.

Autopsy No. 10911: Male, 6 years. Well nourished. Visual disturbances. Typical adamantinoma compressing optic chiasm and invading third ventricle.

Autopsy No. 11198: White female, 32 years. Amenorrhoea. Obesity. Polyuria for $2\frac{1}{2}$ years. Loss of visual activity; diplopia, choked discs, drowsy. Typical adamantinoma extending into third ventricle above the sella. Hypophyseal stalk intact and tumor extends along it.

Autopsy No. 12507: White male, 11 years. Bilateral loss of vision; papilledema, frontal headache and vomiting. Hypophyseal duct cyst with cholesterin crystals extending into floor of third ventricle and into sella. Hypophyseal cells practically normal.

Autopsy No. 12587: White male, 37 years. Obesity developed when 1 year old. Bifrontal headaches, loss of libido and developed female habitus with mild polyuria. Tumor involving third ventricle and compressing hypophysis. Typical adamantinoma.

Autopsy No. 13504: White female, 42 years. Loss of vision beginning when one year of age. No polyuria. Adamantinoma removed from behind optic chiasm, extending along meninges from hypothalamic region. Typical adamantinoma with slight keratinization.

Autopsy No. 13666: White male, 9 years. Headache, vomiting and failing vision. Optic atrophy and papilledema. Urine normal. Tumor at floor of third ventricle, cystic with cholesterin crystals. The tumor is chiefly in the third ventricle and surrounded by glia. Hypophysis seems normal but part of the tumor surrounds the upper part of stalk (fig. 4).

Autopsy No. 15289: White female, 4 years. Headache, vomiting, convulsions, unconscious. Well nourished. Cystic tumor invading hypophysis, optic nerves invaded. Typical adamantinoma with excess keratinization and abundant cholesterol crystals.

Autopsy No. 16973: White male, 30 years. Frontal headaches, defective vision, no polyuria. Bilateral optic atrophy. After removal of suprasellar tumor, polydipsia, disorientation. Compression of optic chiasm and mammillary bodies. Sella and hypophysis flattened by tumor mass. Typical adamantinoma.

From these histories there stands out a series of symptoms which are of mechanical origin—the extreme headaches, the visual disturbances from pressure on the optic chiasm and nerves, other nervous disturbances which are slight and variable, drowsiness and repeated vomiting. Most interesting, from the pressure on the hypophysis or from the involvement of its pars intermedia and stalk, or at any rate from some pressure disturbance of its function, the appearance of the so-called Fröhlich's syndrome in which there is obesity, loss of activity of the sexual organs, and tendency toward a feminine habitus with change in distribution of hair, etc. This was particularly striking in the case described here (Autopsy No. 17551).

The term adamantinoma, or ameloblastoma, is, of course, derived from the similarity or identity of the marginal cells with their cylindrical form and palisade arrangement as they stand against the stroma, with the secreting cells of the enamel organ of the teeth which are also cylindrical, in palisade arrangement and have behind them the stellate reticulum of separated epithelial cells with their delicate processes. They differ, however, in that these cylindrical cells produce no enamel and further in that the stellate reticulum in the origin of the teeth does not produce such concentric masses of squamous epithelium with its keratinization and later calcification which is so regular in the adamantinoma.

The exact mode of displacement of the enamel organ from the natural region of the jaws into that of the hypophyseal duct in the roof of the mouth is not very easily explained in such a large number of cases, but even more difficult is the explanation of the formation of adamantinomas, or ameloblastomas, in the tibia which has been repeatedly observed. The possibility is suggested that in spite of the close resemblance of the marginal cylindrical cells in palisade arrangement to those of the enamel organ, the aberrant behavior of the remaining tumor cells with their keratinization and calcification and production of cholesterol crystals, might lead to an explanation of their origin from some other source such as a distorted development from the Rathke's pouch.

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THE UTERINE ELECTROCARDIOGRAM

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During the course of studies on the fetal electrocardiogram an opportunity presented itself to take electrocardiograms of an infant before, during and after Caesarean section. The technique for recording satisfactory fetal electrocardiograms had been developed by one of us (1) and the taking of a baby's electrocardiogram immediately after birth presented no difficulties; but the recording of fetal deflections during the performance of a Caesarean section presented a problem which had not hitherto been attacked. The fetal record, if obtained, might provide interesting information on the fetal heart and on the effect of anesthesia and surgical procedure on the cardiac mechanism.

CASE REPORT

The patient, W. L., was a thirty-three year old negress in the thirty-eighth week of her pregnancy. She had been observed for a considerable period of time on the medical service. The diagnosis was pulmonary tuberculosis with massive effusion. Tubercle bacilli had been found in the aspirated fluid. The course of the disease had been progressively downhill and it was felt that she could not possibly survive a normal delivery.

A rapid Porro-Caesarean was performed. It was in the course of this procedure that the opportunity presented itself for obtaining our interesting records. It should be noted that the experimental procedure did not add either to the operating time or to the risk involved. The operation was performed under general anesthesia. All other surgical details are irrelevant to the purposes of this presentation.

Preliminary routine fetal electrocardiograms were taken 6 days before the operation and about 2 hours before the patient entered the delivery room. These records are shown in figure 1. In the first record, taken February 25, 1941, the fetal rate is 184 beats per minute, the maternal rate is 132. In the record taken March 3, 1941, the fetal rate is 170 and the maternal rate is 124. Except for the rapid rates these curves are essentially normal.

The problem of recording fetal deflections during the course of the operation was primarily a matter of providing sterile electrodes and applying them to the exposed uterus. German silver electrodes, of the type used with the Cardiette, were attached to six foot lengths of nickel wire. The first three feet of wire, nearest the electrode was covered with rubber tubing. The electrodes with the wire attached and coiled in a small spiral, were sterilized in an autoclave and during the course of the operation, after the abdominal wall had been divided and the intact uterus had been well exposed, these electrodes were applied directly to the moist uterus. The surgeon was isolated from the electrodes by his rubber gloves and by a dry gauze pad with which he held each electrode. The ends of the six foot lengths of nickel wire were brought well away from the operating table and were connected to the lead wires of the electrocardiograph, a specially built cardiette, previously described (2).

Figure 2 shows the fetal electrocardiogram recorded with electrodes applied directly to the unopened uterus. The upper curve was taken with electrodes placed longitudinally, the lower with electrodes placed transversely. The deflections recorded are due solely to the fetal heart. The maternal heart produces no deflection of the galvanometer because both electrodes are on the uterus which is exposed.

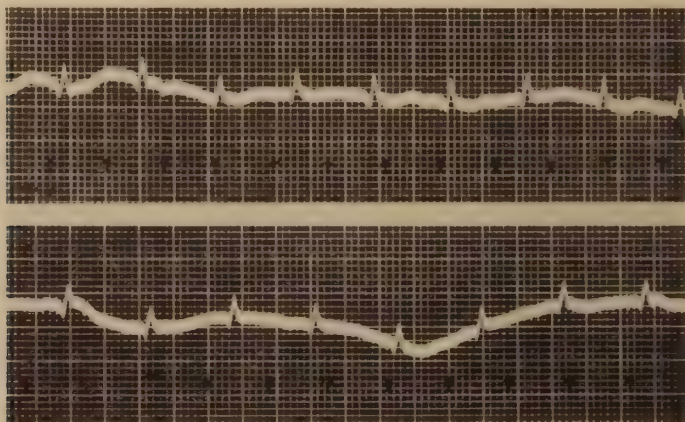


FIG. 1. Fetal electrocardiograms taken 6 days prior to operation (upper curve) and 2 hours before operation (lower curve). Electrodes are placed on the mother's abdomen. Standardization is six centimeters per millivolt. Maternal deflections are large. Fetal deflections, indicated by arrows, are smaller and more rapid.

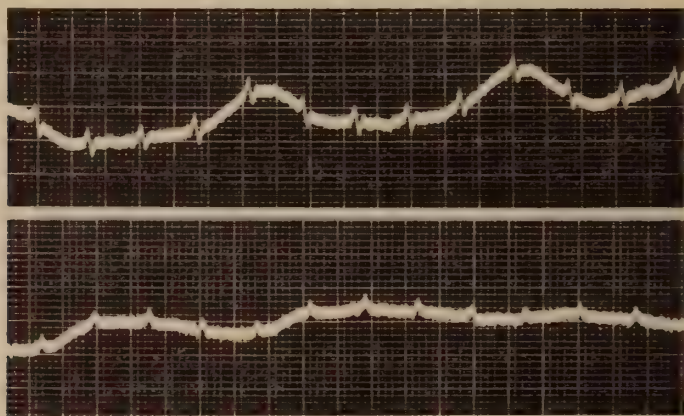


FIG. 2. Fetal electrocardiograms taken during Caesarean operation with uterus exposed and electrodes applied directly to the fundus. In the upper curve the electrodes are applied longitudinally, in the lower curve transversely. Standardization is six centimeters per millivolt. Maternal respiratory movements can be recognized but no maternal electrocardiogram is visible.

This is analogous electrically to placing both electrodes on one limb in which case no electrocardiographic deflection appears.

Figure 3 shows the electrocardiogram of the baby, a female, immediately after removal from the uterus and after normal breathing had been established. Electrodes were held against the two arms and left leg of the infant by dry sterile pads

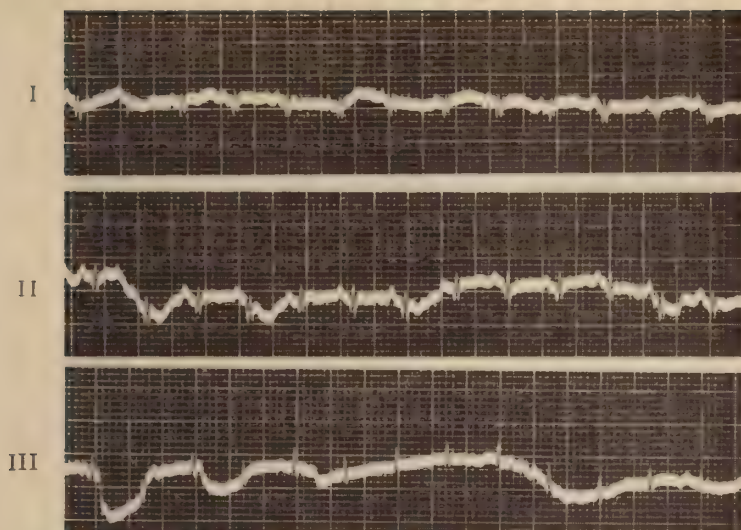


FIG. 3. Infant's electrocardiogram immediately after birth. Standardization is one centimeter per millivolt in this and all following curves. P waves are visible. P-R is short. T waves are not discernible. There is right ventricular predominance.

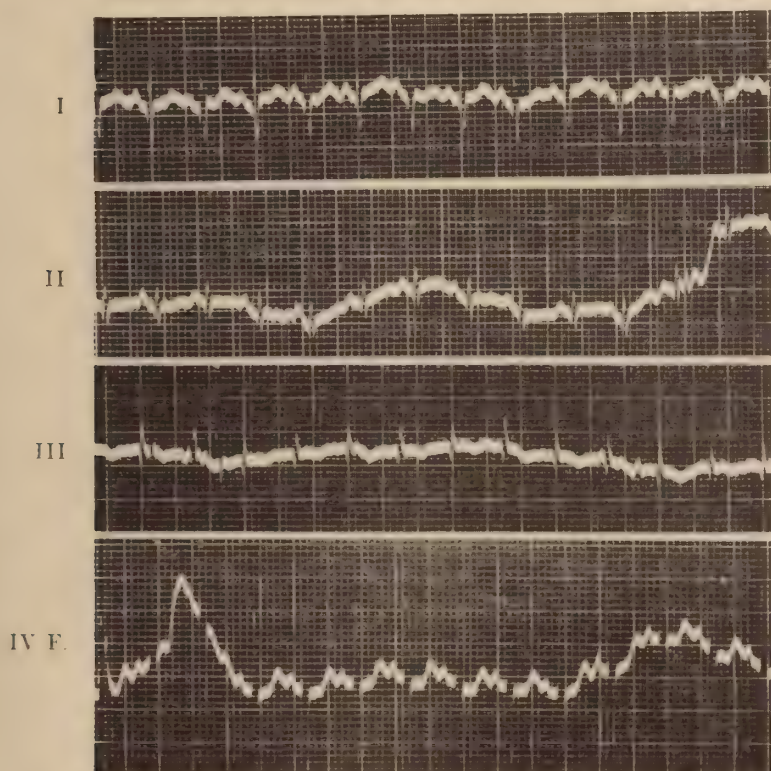


FIG. 4. Infant's electrocardiogram taken about 5 minutes after the previous report. T waves are now visible.

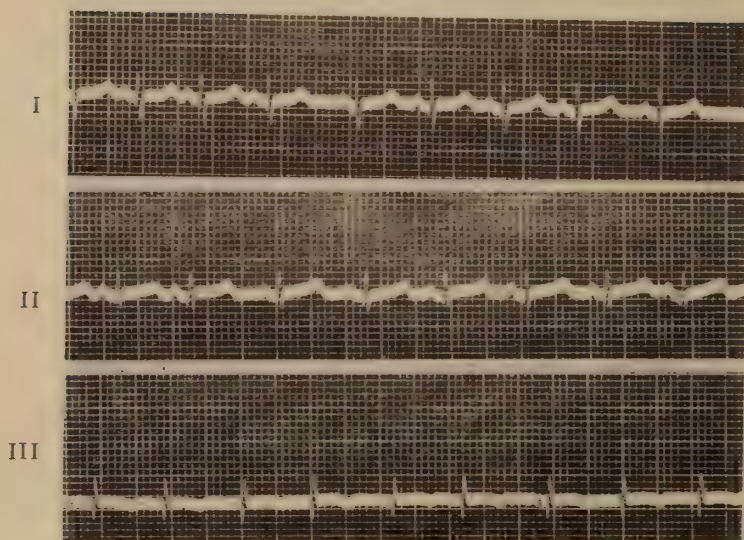


FIG. 5. Infant's electrocardiogram taken 3 days after delivery. The rate is now much slower and the T and P deflections are well formed.

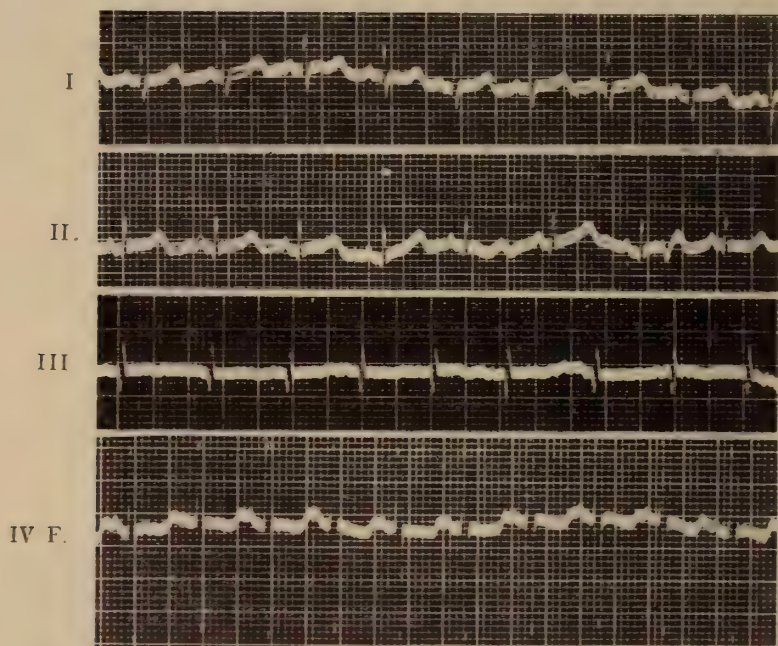


FIG. 6. Electrocardiogram of infant 2 weeks after delivery. The main deflection is now almost completely upright in lead I.

in the hands of an assistant. The heart rate varies from 191 to 199 beats per minute and the main deflection is almost completely inverted in lead I, partly inverted in lead II.

Figure 4 shows the infant's electrocardiogram taken approximately five minutes after the previous record. There has been considerable change in the shape and size of the main deflection within the first few minutes after birth. The fourth lead, taken from the left leg to the apical region, presents the usual configuration. The heart rate varies from 191 to 201 beats per minute.

Figure 5, taken 3 days after birth, shows a rate varying from 131 to 147 beats per minute with considerable sinus arrhythmia. The main deflection is still semi-inverted in lead I.

Figure 6, taken 2 weeks after birth, shows a main deflection which is now only one-third inverted in lead I.

DISCUSSION

It is interesting to note that, except for a slight possible increase in rate, the operation had no obvious effect on the fetal heart. At no time, either before, during or after the Caesarean operation was any conductive disturbance recorded. Except for moderate sinus arrhythmia the rhythm was regular.

It is also interesting that the simple technique of applying two metal electrodes directly to the uterus permits recording of a fetal electrocardiogram much larger and clearer than the record obtained with electrodes on the abdomen. The main deflection is readily observed. P and T waves are not visible.

A further observation of interest is the fact that with both electrodes on the unopened uterus only the fetal deflections are recorded. Apparently the limited area of attachment of the uterus to the maternal body causes the exposed uterus to behave electrically like an extremity. Just as in the arms, legs or head there is no appreciable electrocardiogram recorded when both electrodes are applied to the same extremity, so the uterus, when exposed, seems to act electrically like an extremity with respect to the maternal heart. With respect to the fetal heart exposure of the uterus seems to offer satisfactory conditions for recording the fetal electrocardiogram.

The first appearance of measurable P and T waves in this series of records is directly after birth. The P-Q interval is about 0.08 seconds and after 2 weeks is only 0.09 seconds although the heart rate has fallen to about 130 per minute. The T waves which are small immediately after birth become larger within the next 5 minutes and 3 days later are easily observed. The fourth lead, taken from the left leg to the apical region presents upright P and T waves 5 minutes and 2 weeks after birth.

SUMMARY

1. A series of electrocardiograms were taken of a fetus *in utero* 6 days before a Caesarean operation, of the fetus *in utero* during the operation, after the uterus had been exposed and of the infant at intervals after birth.

2. Electrodes placed directly on the exposed uterus gave a clear fetal curve without any perceptible maternal deflections.

3. General anesthesia and the operative procedure produced no obvious change in the rate or rhythm of the fetal heart.

4. Changes in the infant's electrocardiogram during the first few weeks are recorded in serial electrocardiograms.

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URINARY EXCRETION OF CAPON COMB GROWTH PROMOTING SUBSTANCES IN GRAVES' DISEASE AND MYXEDEMA AND MODIFICATIONS FOLLOWING IODINE AND DESICATED THYROID THERAPY

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What the primary endocrine up-set is that starts the vast endocrine imbalances which characterize Graves' disease still remains unknown. Intensive study of the thyroid hypothesis for 25 years, beginning with Moebius (1) in 1886, has resulted in establishing definitely that the thyroid gland is not the primary site of the disease, and that the goiter is only a sign or a compensatory response to some more distant and complex source of stimulation.

Since 1910 much evidence has been accumulated suggesting that a disturbance in the hormonal interrelations of the adrenal cortex and sex glands precedes the hypophyseal and thyroidal reactions. The sex glands (including adrenal cortex) have appealed to the writer as of fundamental importance in the etiology of Graves' disease for many years (2, 3). Prominent general features of Graves' disease are the sex incidence of around 4 to 1 and the striking association with the menopause, whether natural or artificial (surgical and x-ray). Some experimental data have been published bearing on these questions, particularly the adrenal cortex, and in the present paper some of our data on the excretion of androgenic substances in the urine of persons with Graves' disease are reported.

Method. We have used the very simple and proven-efficient method of Dingemanse, Borchardt and Laqueur (4) for the extractions. Essentially, this consists of collecting the 72 hour urine under benzene as a preservative, then adding 100 cc. of concentrated hydrochloric acid per liter of urine slowly while stirring. Benzene to one-third the volume of urine is added and refluxed for 6 hours. After cooling (usually over night) the benzene is removed and fresh benzene in the same amount is added and the urine again refluxed for 6 hours. The two extracts are combined and the benzene distilled off under reduced pressure to dryness. The extract is then taken up in 100 cc. of absolute alcohol and stored in an ice box until assayed. In the experiments reported here whole extract was used, that is, no separation of the estrogens was attempted.

We have used the Fussgänger (5) modification of the capon comb test. After the dilution to be used for a given extract (1:200-1:2500) was decided upon, the extract was taken up in mazola oil so that 0.5 cc. contained

the total dose of extract per bird. This was painted on the comb in 0.1 cc. doses daily and the final comb measurement (height plus length) taken on the sixth day. Three birds were used for each assay and in practically all instances two or more assays of each extract were made at different times, that is, one assay was usually made soon after extraction and a second assay made after all the urine specimens on a given patient had been extracted.

TABLE 1
Control urine extractions

SEX, AGE, CLIN. DIAG.		URINE SPEC. NO. 72 HRS. VOL.	TOTAL ANDRO- GEN AS ANDROS- TERONE	ANDRO- GEN PER LITER	BMR	MEDICATION
		cc.	mg.	mg.		
E. Male, 18; Rheu- matic heart disease	1	1285	16.67	12.92		None
		1285	14.90	11.60		257 mg. KI added to urine before extraction
		1410	16.07	11.40		Lugol's sol. 10 gtt b.i.d. begun 10 days before collection of urine
	2	1410	17.26	12.24		242 mg. KI added to urine before extraction
B. Male, 47; Coronary artery disease	1	1092	2.48	2.27		None
		1092	2.00	1.93		218 mg. KI added to urine before extraction
		1080	2.08	1.93		Lugol's sol. 10 gtt b.i.d. begun 10 days before collection of urine
	2	1080	2.00	1.85		216 mg. KI added to urine before extraction
B. Male, 12, Obesity (Froelich ?)	1	2290	7.68	3.35	-25	None
	2	2920	6.7	2.29	-12	Rec'd. 2 gr. des. thyroid daily for 10 days prior to and during urine collection
R. Female, 43; Surg. castrate	1	3660	1.46	0.40	+11	None
	2	4740	1.37	0.29	?	Rec'd. 2 gr. des. thyroid daily for 10 days prior to and dur- ing urine collection

Androsterone controls (using 5 to 10 gamma in 0.5 cc. of mazola oil per bird) were run with every urine specimen assayed.

Control urines. Since all patients with Graves' disease received iodine therapy after the initial urine collection, it seemed desirable to determine in non-Graves' patients whether adding iodine to the urine before extraction or whether the prolonged feeding of iodine or desiccated thyroid before collecting the urine altered the amount of capon comb growth promoting

material that could be extracted. The data of four such experiments are given in Table 1. In one case an 18 year old male with rheumatic heart disease was used. The 72 hour urine was divided into equal portions and to one portion 257 mg. of potassium iodide were added to the acidified urine just before the extraction. The assay of this extract showed that the addition of potassium iodide made no significant difference in the amount of androgenic substances extracted. This patient was then given 10 drops of Lugol's solution by mouth twice daily and after 10 days a 72 hour collection of urine was begun. Before extraction, this urine was also divided into equal parts and to one of them 242 mg. of potassium iodide were added. Again no significant difference in the amount of androgenic material extracted was found between the 2 portions of this urine, nor did the administration of Lugol's solution make any significant difference in the results.

A second cardiac patient was studied in the same way. This patient was 47 years old and his disability was due to coronary artery disease. Again no significant difference in the amount of extractable androgen could be made out whether potassium iodide was added to the urine before extraction or whether Lugol's solution had been administered to the patient daily for 10 days before and during the three-day collection of urine.

These two patients also illustrate an average normal and a very low urinary excretion of capon comb growth promoting substance. The urines from several other patients without Graves' disease have been examined before and after iodine medication with results similar to the above, and one may conclude that adding iodide to the urine before extraction or the prolonged administration of iodine to patients *per se* does not significantly influence the amount of capon comb growth promoting substances that can be extracted.

The third patient, an obese boy of 12 years with a possible diagnosis of Froelich's syndrome and repeated basal metabolic rates of minus 20 to minus 25, was given 2 gr. of desiccated thyroid daily, 10 days before and also during the collection of the second three-day urine.

The fourth patient was a female, aged 43, surgically castrated 7 years earlier. After a control 72 hour urine was collected the patient was given 2 gr. desiccated thyroid for 15 days before the second 72 hour urine collection was started.

The volumes of the urine collections before and after desiccated thyroid administration suggest a slight diuretic effect of the thyroid medication, and the capon assays in both cases also suggest a slight reduction of doubtful significance in the excretion of androgenic substances following the administration of desiccated thyroid. If this is a decrease it is the opposite effect of that which we obtained by feeding desiccated thyroid to cases of myxedema.

Data on Graves' disease. In Table 2 we have collected the significant data on the excretion of capon comb growth promoting substances in the

TABLE 2
Graves' disease—urine extractions

SEX, AGE, CLIN. DIAG.	URINE SPEC. NO., 72 HRS. VOL.	DAYS BE- TWEEN URINE COLLEC- TIONS	TOTAL ANDRO- GEN AS ANDROS- TERONE	ANDRO- GEN PER LITER	BMR	MEDICATION
	cc.		mg.	mg.		
S. Male, 30; com- plete Graves'	1. 4630		12.50	2.70	+32	None
	2. 3620	13	10.12	2.80	+19	Lugol's sol. 10 gtt b.i.d. Quin. hydrobr. 5 gr. t.i.d. for 12 days
	3. 4730	35	8.16	1.73	+6	Lugol's sol. 10 gtt b.i.d. Quin. hydrobr. 5 gr. t.i.d. for 12 days
J. Male, 52; Graves' and Parkinsonism	1. 3160		25.50	8.50	+40	Lugol's 4 gtt b.i.d. for 14 days
	2. 2410	47	22.41	7.47		Lugol's 4 gtt b.i.d. for 35 days Lugol's 10 gtt b.i.d. for 12 days; quinine hydrobr. 5 gr. t.i.d.
	3. 2860	74	18.1	6.03		Lugol's 10 gtt b.i.d.; quinine hydrobr. 5 gr. t.i.d.
	4. 2880	49	11.0	3.67		Lugol's 10 gtt b.i.d. quinine hydrobr. 5 gr. t.i.d.
B. Male, 43; Tu- berculosis, tho- racoplasty atyp- ical Graves'	1. 3450		16.12	4.67	+41	None
	2. 2310	10	17.35	6.51	+32	I ₂ (NaI) 6 mg. for 10 days
	3. 3870	20	13.81	3.57	+18	I ₂ (NaI) 125 mg. b.i.d. for 20 days
	4. 3800	8	13.2	3.47	+17	Lugol's 10 gtt b.i.d.; triple bromide 15 gr. daily
	5. 2810	25	17	6.05	+16	Lugol's 10 gtt b.i.d.; triple bromide 15 gr. daily
	7. 2680	208	12.2	4.55	-12	Lugol's 10 gtt b.i.d.; triple bromide 15 gr. daily
C. Female, 53; Complete Graves'	1. 5190		2.85	0.55	+37	None
	2. 5600	10	1.85	0.33	+6	Lugol's 10 gtt b.i.d.; quin. hydrobr. 5 gr. t.i.d.
	3. 5480	25	1.77	0.32	-2	Lugol's 10 gtt b.i.d.; quin. hydrobr. 5 gr. t.i.d.
F. Male, 29; Mild Graves'	1. 4110		19.8	4.82	+42	None
	2. 3610	31	15.5	4.29	+25	Lugol's sol. 10 gtt b.i.d.; quin. hydrobr. 5 gr. b.i.d.
	4. 5000	124	8.26	1.65	-10	Lugol's sol. 10 gtt b.i.d.; quin. hydrobr. 5 gr. b.i.d.
S. Male, 32; Severe complete Graves'	1. 5200*		20.6	3.96	+73	None
	2. 5360†	69	11.3	2.11	-7	Lugol's sol. 15 gtt b.i.d.; quin. hydrobr. 5 gr. b.i.d.

TABLE 2—*Concluded*

SEX, AGE, CLIN. DIAG.	URINE SPEC. NO., 72 HRS. VOL.	DAYS BE- TWEEN URINE COLLEC- TIONS	TOTAL ANDRO- GEN AS ANDROS- TERONE	ANDRO- GEN PER LITER	BMR	MEDICATION
	cc.		mg.	mg.		
A. Male, 37; Graves' and pul- monary tuber- culosis	1. 4080 2. 4060	79	3.15 1.45	0.77 0.35	+29 +3	None
G. Female, 7; Complete Graves'	1. 2520 2. 2985 3. 2760 4. 1785 5. 2220 6. 2480 7. 1840	13 26 24 179 146 107	2.5 1.49 0.50 0.23 0.32 0.73 0.26	0.99 0.50 0.18 0.13 0.14 0.29 0.14	+42 +26 -3 +30 +8 — -19	None 6 gtt Lugol's sol. daily 6 gtt Lugol's sol. daily None 6 gtt Lugol's sol. b.i.d. 5 gtt Lugol's sol. once daily 5 gtt Lugol's sol. once daily
Y. Male, 51; Graves' and ac- tive tuberculosis	1. 3020 2. 2120	21	13.0 6.43	4.30 3.03	+56 +18	None 125 mg I ₂ (KI) b.i.d.
S. Female, 44; menopausal Graves'	1. 4360 2. 3660 3. 4240 4. 3700 5. 2610	21 85 93 35	10.2 5.33 5.89 2.55 2.65	2.34 1.46 1.39 0.69 1.01	+33 +32 +15 +15	None Lugol's sol. 10 gtt b.i.d. and triple bromide Lugol's sol. 10 gtt b.i.d. and triple bromide Lugol's sol. 15 gtt b.i.d. and triple bromide Lugol's sol. 15 gtt b.i.d. and triple bromide

* 48 hrs.

† 60 hrs.

urine of 10 representative cases of Graves' disease ranging in age from 7 years to 53 years. Seven of these were males.

In all instances the urine collection (72 hours unless otherwise stated) was made before iodine medication was started. Usually quinine hydrobromide was also administered with the iodine. At least one, and in one case six, subsequent collections of urine were assayed for comb growth promoting substances.

With one exception (a bilateral cryptorchid, aged 43) there has been a drop in the amount of comb growth promoting substances in urine along with the usual drop in basal metabolic rate and pulse rate following iodine medication. In this patient there was a moderate drop in the basal metabolic rate and general clinical improvement during the first 63 days of observation, but no significant drop in the excretion of androgenic sub-

stances occurred during this period. This patient was tuberculous with a positive sputum beginning in 1931. In 1938 a thoracoplasty operation was done in Montefiore Hospital. Following this he gained rapidly but 6 months later he began to complain of weakness, tremor, sweating, loss of weight and anorexia. The basal metabolic rate at this time was plus 39 and plus 41 per cent. One month later the basal metabolic rate was plus 41 per cent, with the pulse rate averaging about 100 per minute. Exophthalmos was never present, nor was thyroid enlargement ever noted. A complete clinical recovery from Graves' disease occurred in 6 months after iodine medication was started and there has been no recurrence during the past two and a half years. These data are mentioned spe-

TABLE 3
Myxedema—urine extractions

SEX, AGE, CLIN. DIAG.	URINE SPEC. NO., 72 HRS. VOL.	DAYS BE- TWEEN URINE COL- LEC- TIONS	TOTAL ANDRO- GEN AS ANDRO- STER- ONE	ANDRO- GEN PER LITER	BMR	MEDICATION
	cc.		mg.	mg.		
S. Female, 50; Myxedema	1. 6850		0.86	0.12	-23	None
	2. 6690	93	4.00	0.60	+14	Des. thyroid 1 gr. daily for 83 days
	3. 5570	56	3.50	0.63	-1	Des. thyroid 1 gr. daily
N. Male, 54; Mild myxedema	1. 2810		1.11	0.39	-22	None
	2. 4380	47	3.26	0.74	-4	Des. thyroid $\frac{1}{2}$ gr. daily for 32 days
S. Female, 56; Typical myx- edema	1. 3590		0.69	0.19	+4	Des. thyroid 3 gr. daily for over a year
	2. 2980	57	0.89	0.30	+5	Des. thyroid 3 gr. daily
	3. 3310	121	0.85	0.26	+5	Des. thyroid 3 gr. daily

cifically to indicate that this patient never had a complete Graves' disease syndrome although in the opinion of the clinical staff he was classified as Graves' disease.

Another case is of interest because of her age and several exacerbations of the disease. A. G., aged 7 years, was a complete case of Graves' disease with marked progressive exophthalmos. Three months before our observations began she had had a partial removal of both lateral thyroid lobes, not only without any improvement but the disease progressed more rapidly. There had occurred marked regeneration of the thyroid gland. This patient had 2 exacerbations during our experiments after reducing or stopping the iodine medication, and in one of these relapses there was a coincident rise in the excretion of androgenic substances, but for more than

two years she has remained a completely arrested case associated with marked regression of the thyroid gland and exophthalmos.

Data on myxedema. We have had an opportunity of studying the urinary excretion of androgenic substances in 3 cases of Gull's disease—two females and one male. The pertinent data are given in Table 3. One of these patients had been on a maintenance dose of desiccated thyroid for 2 years before we began our studies and this medication was continued over the whole period (178 days) of our observations. It is significant that the excretion of androgenic substances during the 3 three-day urine collections was always extremely low, yet fairly uniform in amount.

In the other 2 cases control three-day urines were obtained before desiccated thyroid medication was started. Neither was a severe case of myxedema as judged by the clinical condition and the basal metabolic rate. The total excretion of capon comb growth promoting substance in the control urine was 0.86 mg. in the female and 1.11 mg. in the male. The second three-day urine, taken in one case after 83 days of thyroid medication and in the other cases after 47 days, showed a significant rise in the total amount of androgenic substance excreted, although still not more than one-quarter of the average normal excretion. These findings are in striking contrast with those of Graves' disease where iodine medication caused a sharp drop in the amount of androgenic substance excreted.

DISCUSSION

While an enormous but inconclusive literature exists on the relation of the sex glands to Graves' disease, it is striking that up to the present time no systematic studies have been made on the excretion of sex hormones in relation to any phase of this disease. Laurent-Gerard and Welti (6) reported upon the estrogenic hormone excretion in 6 cases of Graves' disease in women. Following subtotal thyroidectomy they found a rise in both the blood and urinary estrogen in 4 cases and no change in 2 cases. One of these 2 cases was a post-menopausal Graves' disease and the other had normal levels of blood and urinary estrogen before operation. The reactions observed are probably mediated through the hypophysis.

Our studies on the excretion of androgenic substances in cases of Graves' disease indicate that there are very wide variations in the quantity appearing in the urine in different patients. This suggests a relative, rather than an absolute, increase in the excretion of the androgenic material. Iodine administration in most of the cases but not in all cases that were diagnosed as hyperthyroidism caused a drop in urinary excretion of androgenic material. This drop was coincident with other evidence of clinical improvement. No adequate explanation for this drop is at present available. Two control experiments with non-Graves' patients showed that the administration of similar amounts of iodine did not decrease the urinary androgen. Nor does the addition of iodine to the urine at the time of

extraction alter the amount of extractable androgenic material. Also feeding desiccated thyroid to the point of raising the metabolic rate in 2 non-Graves' cases lowered the amount of extractable androgens only slightly, if at all, although in 2 cases of myxedema the administration of desiccated thyroid definitely increased the urinary excretion of androgenic substances. It is, therefore, obvious that the effect of large doses of iodine in lowering the excretion of androgenic substances in many cases of Graves' disease is not due to inactivation of the androgen either *in vivo* or *in vitro*, nor is it due to preventing the formation of androgenic substances in the gonad, although some observers have claimed that iodine causes an involution of the interstitial cells in guinea pigs (7). We have carried out 3 series of such experiments in guinea pigs with entirely negative results.

It is characteristic of Graves' disease that the interstitial cells of the testes are well preserved, indeed some reports claim an hypertrophy. This is in contrast with myxedema where the interstitial cells appear definitely involuted and possibly decreased (8). A decrease in the production of estrogenic substances has for years been suggested because of the striking increase in the incidence of Graves' disease at the menopause, both natural and induced. On the other hand, so far as we can find, no one has yet reported a case of Graves' disease in a male castrate. There are, however, several reports of myxedema in the male following castration.

It is known that the administration of testosterone will cause thyroid hyperplasia. We have many times observed this in rabbits. Natural estrogenic substances, on the other hand, definitely depress the thyroid gland. It is also certain that testosterone will greatly increase an existing exophthalmos in rabbits and produce a recurrence of the exophthalmos in rabbits in which the exophthalmos has receded following castration (9). In this connection it is a suggestive association that the exophthalmos of Graves' disease is usually more marked during menstruation at which time the level of estrogenic substances in the blood is lowest and that of androgenic substances is relatively highest.

Of the 3 cases of Gull's disease, all excreted very small amounts of androgenic substances. Two had had no previous treatment and showed a significant rise in the amounts of capon comb growth promoting substances excreted in the urine following the administration of desiccated thyroid. The literature records numerous instances of Gull's disease in females (10) where sex cycles were restored following treatment with desiccated thyroid. Cases of Gull's disease in males are also reported where sexual activity was restored by thyroid feeding. McCullagh (11) has recently reported such a case. In view of our observations it is reasonable to assume that an increase in the production of androgenic substances following desiccated thyroid therapy was also present in the cases cited from the literature.

Where the increase in androgenic material is produced is not known. However, since the thyroid gland is known to be closely interrelated with the adrenal cortex it is possible that the latter may be the chief source (12, 13, 14, 15).

SUMMARY

Data are presented which indicate that the administration of large amounts of iodine does not depress the urinary excretion of androgenic material in non-Graves' patients, but usually does so in cases of true Graves' disease, particularly if there is other evidence of clinical improvement. Desiccated thyroid administration to the point of elevating the basal metabolic rate does not definitely lower the amount of androgenic substance excreted in non-myxedema patients but did cause a significant rise in the two cases of Gull's disease studied. In Graves' disease the absolute amount of androgenic substances excreted in the urine varies widely. In some cases it is approximately normal but more often it is reduced; so that if the amount of androgenic substances excreted is significant it can only be a relative increase creating an imbalance in the realm of the steroid hormones and it may be that one of the causes for improvement of patients with Graves' disease following partial thyroidectomy is that it aids in correcting such an imbalance.

In Gull's disease there appears to be an absolute decrease in the urinary excretion of androgenic substances which may be raised by treatment with desiccated thyroid.

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NOMENCLATURE OF CORONARY ARTERY DISEASE: THE DIFFERENTIATION OF ANGINA PECTORIS, CORONARY INSUFFICIENCY AND CORONARY OCCLUSION

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In the past acute episodes due to coronary disease were called angina pectoris when the attack consisted of a short bout of substernal pain without clinical findings and with evanescent, if any, electrocardiographic changes, and were called coronary thrombosis when the attack was associated with prolonged pain, signs of shock and heart failure, changes in the heart sounds, a drop in blood pressure, pericarditis and progressive alterations in the electrocardiogram.

In recent years numerous clinical, electrocardiographic and pathological studies (1 to 14) have added much to our knowledge of coronary disease and have demonstrated that infarction of the myocardium may occur without coronary closure, i.e., acute coronary insufficiency. This concept has introduced the problem of nomenclature and confusion of the entire field has been threatened by several writers (12, 14, 15) who advocate that the term coronary occlusion be replaced by myocardial infarction, coronary insufficiency or coronary failure, on the ground that coronary occlusion is merely an extreme instance of coronary insufficiency. We believe, however, that the term coronary occlusion should be retained since it is a well defined clinical and electrocardiographic syndrome. The term coronary insufficiency should be restricted to myocardial infarction or necrosis without occlusion since it is usually associated with specific anatomic and electrocardiographic alterations (2, 13) although it may resemble coronary occlusion clinically. It seems to us fruitless to label all forms of acute coronary disease "coronary insufficiency" or "coronary failure" when coronary occlusion and coronary insufficiency in the limited sense described can usually be distinguished by the clinical features and almost always by the electrocardiogram (2, 13).

The specific electrocardiogram of coronary occlusion consists of deep Q waves and RS-T elevations; there is a reciprocal relationship between leads I and III. In anterior infarction (fig. 1A) the Q waves and RS-T elevation are present in leads I and IV, in posterior infarction they occur in leads II and III (fig. 1B). There is a progressive pattern of change over a period of weeks, the RS-T elevations giving way to deep T-wave inversions.

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The electrocardiogram seldom returns to normal and may be indicative of coronary occlusion for many years. In coronary insufficiency (2, 13) the electrocardiogram shows depression of the RS-T segment and low, diphasic or inverted T waves in 2 or more leads, chiefly leads I and II (fig. 1C). There is no reciprocal relationship between leads I and III. A deep Q wave or RS-T elevation is rarely encountered and it is distinctly unusual. The changes usually are most prominent in the first record and then

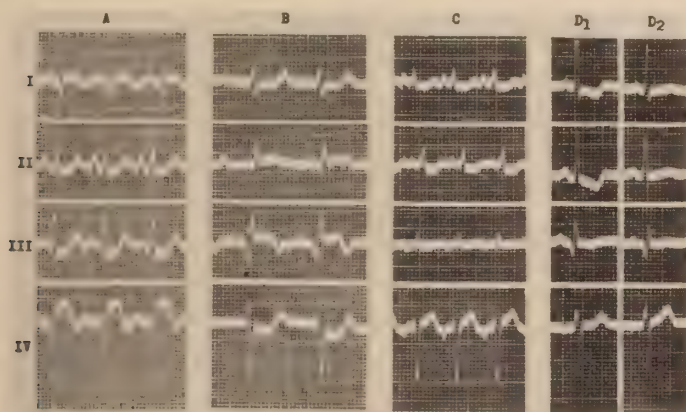


FIG. 1A. L. S. #438516, male, age 42. Electrocardiogram is characteristic of acute coronary occlusion with anterior infarction: large Q_1 , 4, RS-T segments elevated and T waves inverted in leads I and IV. Reciprocal relationship of RS-T and T in leads I and III. Post mortem—acute occlusion of left anterior descending coronary artery with anterior infarction.

B. H. S. #457398, male, age 46. Electrocardiogram is typical of coronary occlusion with posterior infarction: large Q_3 and elevated RS-T segment and inverted T wave in leads II and III. Reciprocal relation of RS-T and T in leads I and III. In lead IV the RS-T segment is depressed. Post mortem—occlusion of right coronary artery with posterior infarction.

C. E. C. #419670, female, age 55. Electrocardiogram indicates coronary insufficiency: RS-T segment is depressed and T wave low in leads I and II. There is no reciprocal relationship in leads I and III. Post mortem—diffuse myocardial necrosis without coronary occlusion; severe coronary sclerosis, pulmonary embolism.

D. M. S. #479952, male, age 43. Angina pectoris due to coronary sclerosis. Electrocardiographic changes of transitory coronary insufficiency induced by exercise. D₁, taken immediately after the exercise, shows depression of RS-T segments and inversion of T waves in the three standard leads, indicating myocardial ischemia. D₂, taken 8 minutes later, no longer shows these alterations and is practically normal.

regress. They last several hours or at most a week or two. The electrocardiogram then returns to its original form.

A characteristic electrocardiogram is not present in every case of coronary occlusion for, if the electrocardiogram is very abnormal to begin with, the advent of a coronary occlusion may add little change. In such a case the electrocardiogram is less helpful than the clinical picture in making a diagnosis. However, what we do wish to emphasize is that when the typical electrocardiographic pattern of coronary occlusion is present, the latter is found post mortem with very rare exceptions.

TABLE 1
Summary of 83 consecutive cases suspected of coronary occlusion

CASE	ADM. NO.	AGE	SEX	ELECTROCARDIOGRAM	POST MORTEM			
					Occlusion	Infarct	Necrosis	Peri- car- ditis
Electrocardiogram—characteristic. Post mortem—coronary occlusion								
1. F. R.	443599	60	M	Posterior	L.C.	+	—	—
2. A. S.	431656	60	M	Anterior	L.A.D.	+	—	—
					L.C.			
3. E. M.	444867	61	F	Posterior	L.C.	+	—	+
4. S. W.	450219	59	M	Ant.-Post.	R.C.	—	+	—
					L.A.D.			
5. I. S.	425318	45	M	Posterior	R.C.	+	—	—
6. M. O.	457838	74	M	Anterior	L.C.	+	—	+
7. E. H.	463375	55	F	Posterior	R.C.	+	—	—
8. J. L.	458053	57	M	Anterior	L.A.D.	+	—	+
9. L. C.	460046	44	M	Ant.-Post.	L.A.D.	+	—	—
					R.C.			
10. S. L.	452172	74	M	Anterior	L.A.D.	+	—	—
11. M. S.	465417	51	M	Posterior	R.C.	+	+	+
12. L. C.	454753	43	M	Anterior	L.A.D.	+	—	—
13. H. D.	446681	43	M	Anterior	L.A.D.	+	—	—
					R.C.			
14. J. S.	443387	47	M	Posterior	L.A.D.	+	—	—
15. H. K.	466751	60	M	Posterior	R.C.	+	—	+
16. M. R.	438083	54	M	Anterior	L.A.D.	+	—	+
17. L. S.	438516	42	M	Posterior	L.A.D.	+	—	+
					R.C.			
18. Z. W.	412881	54	M	Posterior	R.C.	—	+	+
19. J. D.	449072	55	M	Anterior	L.A.D.	—	+	—
20. N. P.	452870	82	F	Anterior	L.A.D.	+	—	—
21. M. H.	429651	72	M	Ant.-Post.	L.A.D.	+ Ant.	+ Post.	+
22. A. K.	430289	59	M	Posterior	R.C.	—	+	—
23. J. M.	387038	65	M	Posterior	R.C.	+	—	—
24. D. B.	398067	56	M	Anterior	L.A.D.	+	—	—
25. B. V.	448363	50	F	Anterior	L.A.D.	+	—	—
26. S. L.	446600	50	M	Anterior	L.A.D.	+	—	—
27. H. B.	406061	62	M	Ant.-Post.	R.C.	+	—	—
28. O. L.	407587	63	M	Ant.-Post.	L.A.D.	+	+	—
29. J. S.	407390	53	M	Anterior	L.A.D.	+	—	+
30. P. S.	390088	55	F	Anterior	L.A.D.	+	—	+
31. J. W.	413699	63	M	Anterior	L.A.D.	+	—	—
32. J. K.	385381	56	M	Anterior	L.A.D.	+	—	—
33. N. D.	392047	60	M	Posterior	L.C.	+	—	+
					R.C.			
34. R. T.	397182	51	F	Anterior	L.A.D.	+	—	—
35. J. L.	399108	67	F	Posterior	R.C.	+	—	—
Electrocardiogram—characteristic or suspicious. Post mortem—no coronary occlusion								
36. R. P.	384075	84	F	Posterior		—	+	—
37. R. S.	385365	70	F	? Posterior		—	—	—
38. S. S.	447331	69	M	? Anterior		—	+	—
39. S. T.	428761	54	M	Anterior		—	—	+

TABLE 1—Continued

CASE	ADM. NO.	AGE	SEX	ELECTROCARDIOGRAM	POST MORTEM			
					Occlusion	Infarct	Necrosis	Peri- card- itis
Electrocardiogram—bundle-branch block. present					Post mortem—coronary occlusion present			
40. G. K.	453380	65	M	BBB Vent. Tachy.	L.A.D.	—	+	—
41. D. F.	383531	75	M	BBB Long P-R	R.C.	+	—	—
42. T. B.	395287	58	M	BBB	L.A.D.	+	—	—
43. W. F.	444679	51	M	BBB, Complete A-V Block	L.A.D. L.C.	+	—	+
44. D. D.	387259	52	F	BBB, Small R ₁	R.C.	+	—	—
Electrocardiogram—non-specific. Post mortem—coronary occlusion present								
45. S. H.	402867	50	M	T ₁	L.A.D.	+	—	—
46. J. L.	381256	62	M	T ₂	L.C.	+	—	—
47. P. B.	386384	67	M	T ₁	R.C.	+	—	—
48. E. A.	455567	48	F	Hypertension	R.C.	+	—	—
49. A. L.	458297	69	M	T ₁₋₄	L.A.D. L.C.	+	—	—
50. A. V.	415936	61	M	T ₁	R.C.	+	—	—
51. A. G.	404952	52	M	T _{1, 4}	R.C.	—	—	—
52. M. H.	449478	85	M	Q ₃ T ₁	R.C.	—	+	—
53. C. B.	434487	68	M	T _{1, 2, 3.}	L.A.D.	—	—	—
54. A. K.	445548	74	M	T ₁₋₅	L.A.D.	+	—	—
Electrocardiogram—non-specific. Post mortem—no coronary occlusion								
55. C. H.	459153	68	F			—	—	—
56. T. B.	433469	62	M			—	—	—
57. E. B.	434121	77	M			—	—	—
58. N. P.	435696	47	M			—	—	—
59. L. S.	461830	70	M			—	—	—
60. L. S.	445536	59	M			—	—	—
61. A. H.	436060	60	F			—	—	—
62. S. B.	410730	55	F			—	—	—
63. B. F.	395731	52	F			—	—	—
64. W. S.	392658	60	M			—	—	—
65. M. K.	434044	48	M			—	—	—
66. T. R.	432200	67	M			—	—	—
67. A. H.	431847	71	M			—	—	—
68. S. P.	463069	62	M			—	—	—
69. R. S.	456510	51	M			—	—	—
70. A. E.	459042	73	M			—	—	—
71. T. S.	467151	57	M			—	—	—
72. M. F.	447501	46	M			—	+	—
73. L. L.	461925	66	M			—	—	—
74. M. R.	451972	60	M			—	—	—

TABLE 1—*Concluded*

CASE	ADM. NO.	AGE	SEX	ELECTROCARDIOGRAM	POST MORTEM			
					Occlusion	Infarct	Necrosis	Peri- car- ditis
Electrocardiogram—non-specific. Post mortem—no coronary occlusion— <i>Cont.</i>								
75. T. A.	427389	45	M			—	—	—
76. S. B.	434527	74	M			—	—	—
77. J. C.	434920	68	M			+	—	—
78. M. W.	421978	71	M			+	—	—
79. E. B.	422603	65	M			—	+	—
80. A. G.	447269	45	M			—	—	—
81. M. R.	449478	85	M			—	—	—
82. B. W.	442487	64	M			+	—	—
83. A. K.	438614	68	M			—	+	—

The typical symptoms and signs of coronary occlusion occasionally are simulated by coronary insufficiency but certain factors usually enable one to distinguish them even without the electrocardiogram (13) (table 1). Coronary occlusion usually occurs at rest and is unrelated to external factors, such as effort and excitement. It is merely an incident in the course of coronary sclerosis. On the other hand coronary insufficiency, while predisposed to by coronary sclerosis, hypertension and cardiac enlargement, may be precipitated by any condition decreasing the coronary flow or increasing the work of the heart, such as effort, emotion, hemorrhage, shock, operation, heart failure, tachycardia, heart block, aortic stenosis or insufficiency, hypertensive crisis. The relative insufficiency of coronary flow may or may not produce cardiac necrosis. In coronary occlusion the pain is usually very severe whereas in coronary insufficiency it frequently is mild or is masked by the underlying condition; indeed, there may be no symptoms at all and the diagnosis is then entirely electrocardiographic. Shock, heart failure, changes in the heart sounds, gallop rhythm, fall in blood pressure, arrhythmias, leucocytosis, fever and rapid sedimentation time are cardinal signs of coronary occlusion; in coronary insufficiency they may be mild or absent. Azotemia and glycosuria are much more common in coronary occlusion. The course of coronary occlusion is usually prolonged whereas the symptoms of coronary insufficiency frequently disappear as soon as the precipitating factor is removed and may last but a few hours.

Coronary occlusion and coronary insufficiency also differ pathologically (2, 8, 13). The former produces a large confluent infarct, often extending from the endocardium to the pericardium; coronary insufficiency may produce no changes in the myocardium, or, if the degree of ischemia is severe and prolonged, usually results in focal disseminated areas of necrosis in the subendocardial layer and papillary muscles; the infarct is small, hardly ever a large one. These anatomical differences explain the diverse

electrocardiographic patterns in occlusion and insufficiency since it has been shown that RS-T elevation, which is found in occlusion, is due to involvement of the pericardium or the outer portion of the myocardium, whereas RS-T depression is associated with changes in the subendocardial layer, as in coronary insufficiency. The anatomical differences also explain the frequency of pericarditis and mural thrombosis with embolization in infarction due to coronary occlusion and their absence in necrosis due to coronary insufficiency.

For statistical purposes we have reviewed the last 83 consecutive post mortem cases in which the diagnosis of coronary occlusion had been suspected clinically (table 1). The average number of electrocardiograms for each case was two. First the cases were divided clinically into three groups: coronary occlusion, coronary insufficiency or neither, as judged from the history, clinical course and electrocardiogram. These results were then correlated with the pathological findings. The method of examining the hearts has already been presented (11, 16). The arteries

TABLE 2

Correlation of electrocardiographic and post-mortem findings in 83 cases suspected of coronary occlusion

ELECTROCARDIOGRAM	NUMBER	AUTOPSY -CORONARY OCCLUSION	
		Present	Absent
Characteristic.....	37	35	2
Suspicious.....	2	1	1
Bundle-branch block.....	5	5	0
Non-specific.....	39	10	29

were minutely examined after cross sectioning at intervals of 2 to 3 cm. This method has disclosed as great a percentage of coronary occlusion as any other method including injection (12). In 37 cases the electrocardiogram was considered characteristic of coronary occlusion, that is, RS-T elevations and deep Q waves were present (table 2). Coronary occlusion was found post mortem in all but two of these cases, that is, in 95 per cent. The two exceptions were pulmonary embolism and coronary insufficiency. Sixteen additional cases died of coronary occlusion: in ten of these the electrocardiogram was not specific, that is, there were QRS and T wave abnormalities but no RS-T elevations or progressive changes; bundle-branch block was present in five and in the remaining one the electrocardiogram was hypertensive in type but was somewhat suspicious of coronary occlusion because of a cove-plane T wave in lead IV. There were 29 cases in which the electrocardiogram did not suggest coronary occlusion and this was not found post mortem. These included cases of acute coronary insufficiency, sudden postoperative death, acute cor pul-

monale, acute heart failure, pneumonia with shock, the clinical course of which raised the suspicion of coronary occlusion. In the final case the electrocardiogram was suspicious, but not typical, of coronary occlusion and the cause of death proved to be pulmonary embolism.

Summarizing the above findings it will be seen that when the electrocardiogram is characteristic of coronary occlusion the latter is found at post-mortem examination in 95 per cent of the cases. The two exceptions were pulmonary embolism and coronary insufficiency. As is well known, the electrocardiogram in pulmonary embolism may simulate that seen in occlusion of the right coronary artery with posterior infarction since lead III may show a deep Q wave and RS-T elevation. In the exceptional case of coronary insufficiency with infarction in the absence of occlusion the electrocardiogram simulated coronary occlusion in that there was a Q wave and RS-T elevation in lead IV. However, an intraventricular defect, another possible cause of these electrocardiographic changes, was also present. It is apparent that coronary occlusion does not always produce a typical electrocardiogram; the alterations in the electrocardiogram may be non-specific since preexisting QRS and T wave abnormalities, bundle-branch block and the pattern of a large left or right ventricle may persist in spite of a fresh coronary occlusion and no, or atypical, acute changes may appear. This applies particularly to bundle-branch block. It should be remembered also that the cases studied in this series were fatal and that many had had previous coronary occlusion resulting in very abnormal electrocardiograms prior to the attack which may mask the acute changes. Also many of the cases had only one or two electrocardiograms; if the patient had lived longer typical changes might have appeared.

Our findings, we believe, justify the retention of the term coronary occlusion since in most cases the clinical picture is typical and the electrocardiographic pattern is pathognomonic. Except in very rare cases it is readily distinguishable from coronary insufficiency in the sense described previously. To be sure, it is theoretically possible to group both of these under the general term coronary insufficiency and to attribute the clinical syndrome and electrocardiographic changes to the resulting infarction. In this scheme coronary occlusion would represent the severest degree of coronary insufficiency. However, we can not see any practical advantage in this suggestion, which tends to obscure the subject. In our opinion it is preferable to retain the term coronary occlusion which is so firmly entrenched in common usage and describes a definite clinical and electrocardiographic entity. In fact, we have observed cases of coronary occlusion with a characteristic electrocardiogram in which occlusion was found post mortem without infarction because the patient had died too soon. Such cases comprised 14 per cent of a large series studied by Horn and Finkelstein (11) at autopsy. Also changes have appeared within twenty minutes after the attack. Certainly, in such cases the electro-

cardiographic pattern cannot be ascribed to infarction. Merely because some cases of coronary occlusion do not reveal the typical electrocardiographic pattern and rare cases of coronary insufficiency present changes usually associated with occlusion is not sufficient reason to discard the concept of coronary occlusion. We have shown that this diagnosis can be made correctly in the overwhelming majority of cases. In the few cases in which it is not possible to make a definite diagnosis the cause of the infarction may be left in abeyance temporarily until it is clarified by the future course of the disease. If there is rapid improvement, particularly in the electrocardiogram, the condition is probably coronary insufficiency. If the changes are slowly progressive it is probably coronary occlusion. In addition to the typical RS-T depression in the electrocardiogram the diagnosis of coronary insufficiency should be suspected when a precipitating factor, such as hemorrhage, shock or aortic stenosis, is present. Such a differentiation is important from a therapeutic standpoint since in myomalacia due to coronary insufficiency prompt treatment of the condition precipitating it may be lifesaving. In infarction due to coronary occlusion such treatment may at times actually be harmful.

It would also seem worthwhile to retain the term *angina pectoris* although it is nothing more than a very transitory attack of coronary insufficiency. It represents a well established clinical syndrome, that is, attacks of substernal pain precipitated by effort, excitement, cold, food, etc. It is relieved by nitroglycerin or disappears as soon as the precipitating factor is withdrawn. Since the coronary insufficiency lasts a short time there are no gross changes in the myocardium and very transient alterations in the electrocardiogram, if any. When present they are typical of coronary insufficiency, consisting of RS-T depression and T wave changes (fig. 1D). There are no changes in the heart sounds and blood pressure, and myocardial failure does not occur.

We suggest the following as a practical nomenclature of acute coronary disease.

1. *Angina Pectoris*—transient coronary insufficiency with typical attacks of substernal or precordial pain on effort and transient or no acute electrocardiographic changes.

2. *Coronary Insufficiency*—a more severe or prolonged degree of insufficiency than *angina pectoris*. It may simulate the latter or be asymptomatic. It is associated with subendocardial areas of necrosis in the myocardium and typical electrocardiographic changes (RS-T depression and T wave inversion) lasting several hours or days. The episode is usually associated with a precipitating factor increasing the work of the heart or diminishing the coronary flow. Clinical symptoms may be absent or may simulate coronary occlusion.

3. *Coronary Occlusion*—complete obstruction of a coronary artery with massive through and through infarction, resulting in a characteristic

clinical picture and electrocardiogram, including Q waves, and RS-T elevations progressing into T wave inversions which persist for a long period.

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OTITIC INFECTIONS DUE TO THE PNEUMOCOCCUS TYPE III

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The peculiar clinical course of otogenous infections due to the Pneumococcus Type III attracts the interest and attention of the internist as well as the otologist. The insidious character of this infection as well as its recognized tendency to produce intracranial complications has been a source of concern ever since Schottmüller (1) described this organism in 1903. He named it *Streptococcus mucosus* because of its mucus-producing property on blood agar cultures. It was his impression that he was dealing with the same organism that Richardson (2) had described two years previously but had called *Pseudopneumococcus*. Since that time the pneumococcus type III has been erroneously classified as a streptococcus and the term *Str. mucosus* has remained more or less fixed in the minds of physicians. In spite of the fact that in 1927 it was definitely established and classified as the pneumococcus type III according to bacteriologic standards of bile solubility, agglutination and precipitation, the organism at the present time is still referred to by some as *Str. mucosus*. It is advisable that this misnomer be abandoned and the correct term—*Pneumococcus type III*—be universally adopted.

Notable is the fact that in 3 of the 7 cases first described by Schottmüller in which this organism was obtained the condition was of otitic origin. In each of these 3 the infection terminated in bacterial meningitis, and the organism was recovered from the spinal fluid. The same author at that time made the interesting clinical observation that the mastoid bone was involved relatively early, that the tympanic membrane showed slight changes and that the meningitis was of a fulminating nature, occurring within one week of the onset of the otitis.

Neumann, Rutin and Gohn (3), in 1909, were among the first to draw the attention of the otologist to the pneumococcus type III. They considered this organism the causative factor in the production of a characteristic clinical otologic picture, with which otologists are more or less familiar at the present time. Since that time, although many references to this subject have been made in the literature both here and abroad, few authors have entered into a comprehensive analytic study of infections by the pneumococcus type III. Thus, there appeared reports of cases of Kruger (4), Moulouguet and Piton (5), Mathe (6), Urbantschitsch (7), Brunner (8) and others. Richter (9), in 1929, and Claus (10), in 1930, published

more detailed reports on this subject. The Japanese authors Ko and Kadiura (11) have contributed papers on the experimental biologic properties of the organism.

Realizing the importance of the pneumococcus type III infection to otology and the relative scarcity of references to this subject in the literature, we have reviewed all the cases of pneumococcus type III mastoiditis observed in the otologic service at The Mount Sinai Hospital during a period of nine years (1929 to 1937 (12)). These totaled 73. Only those cases were included in which a definite diagnosis was established by recovery of the organism on culture of material obtained from the middle ear or the mastoid at operation or of the blood or spinal fluid. From our clinical experience with the type of otologic infection under discussion and from an analytic study of the cases observed, our concept of the varying character of this clinical entity has been further enlarged.

Sex: Of the 73 patients 55 were male and 18 female; a proportion about the same as for the usual otitic infection.

Age: With the exception of a definite preponderance of pneumococcus type III infections in the aged, there was essentially no difference in the age incidence of otitic infections due to this organism and to the streptococcus. Fifty-two per cent of the cases occurred in the fifth, the sixth and the seventh decade. We have also observed that not only is pneumococcus type III otitis relatively less frequent in children than in adults, but it is less virulent. In children the pneumococcus type III does not give the same concern as it does in adults.

It is believed that pneumococcus type III otitic infections are prevalent among those suffering from diabetes or other debilitating diseases. Diabetes was present in 12 of the 73 cases in this series. The impression is gained that the association of diabetes with pneumococcal infections is definitely higher than with other types of otitic infection.

TYPES ACCORDING TO CLINICAL COURSE

In an analysis of the cases we observed, with regard to the clinical course, a division into three groups could be made. A sharp line of demarcation between these groups was not always possible. The following divisions were made:

1. Prolonged insidious clinical course with few or no physical signs, followed by evidence of mastoiditis or intracranial complication (18 cases).

2. The usual clinical course of infection of the middle ear, followed by evidence of mastoiditis or intracranial complication (53 cases).

3. Short clinical course (two to five days), followed by intracranial complications (2 cases).

It should be noted that type 3 corresponds more or less to the type described by Schottmüller (1) in 1903 and to the so-called foudroyante type

reported by Ruttin (13) in 1934. Type 1 is the one to which most frequent reference is made in the literature and with which physicians are most familiar.

SYMPTOMS

While in the majority of cases studied the otitis was ushered in by an infection of the upper part of the respiratory tract, usually of influenzal type (44 of 73 cases), not infrequently no such history was elicited. In 8 instances the otitis set in shortly after swimming.

Pain in the ear or in the mastoid region, commonly observed in streptococcic infections, is also a frequent complaint in this form of otitis. Hemispherical pain was a frequent complaint (44 cases). Pain in the eye was present in 4 cases. Of particular importance was the absence of otalgia throughout the course of the otitis, although signs of mastoiditis or intracranial complication subsequently developed.

Tinnitus or fullness in the ear was present in 11 instances. While it may be associated with other symptoms of otitis media, it is important to remember that it may be the only symptom throughout the illness. Such was the case in 4 instances; in 1 of these treatment for four months before admission to the hospital consisted of catheterization of the eustachian tube, after which aural examination disclosed definite evidence of mastoid involvement.

A not unusual observation which we feel is somewhat characteristic of pneumococcus type III infection is a latent period during the clinical course, followed by a return or exacerbation of symptoms. This was noted in 7 instances.

TYPES ACCORDING TO AURAL SIGNS

The otoscopic picture may be one of the following types:

1. Picture of acute suppurative otitis usually seen in streptococcic infections.
2. Resolving middle ear following a suppurative process. The drum is thickened; landmarks are visible to varying degrees; there is no discharge, and occasionally there is sagging of the posterosuperior canal wall.
3. Dry middle ear—absence of discharge throughout illness (from history).
4. Influenzal picture—blebs on the tympanic membrane and in the external canal.
5. Mucoid discharge from the tympanum throughout the course of the otitis.

Comment on these types. Type 1. Those cases of Pneumococcus type III otitis in which the tympanic membrane resembles that in the usual streptococcic infection present a type 1 picture and are by far the most frequent. Since there are no characteristic changes, the picture being

familiar to all otologists, this group will receive little comment. It must not be construed, however, that this type may not run a prolonged insidious course, or a short clinical course terminating in an intracranial complication (types 1 and 3 according to clinical course, previously described). Because of the resemblance of this otoscopic picture to that seen in the usual streptococcic infection, the importance of determining the type of organism can readily be understood.

Type 2. Acute mastoiditis or intracranial complication in the presence of a resolving middle ear is characteristic of pneumococcus type III infection. In such instances there is a cessation of the aural discharge; the landmarks show evidence of reappearing; radiating vessels can be seen on the drum, and the patient is apparently recovering. Postauricular tenderness may or may not be present. Occasionally there exists sagging of the superior canal wall, associated with spontaneous otalgia or headaches. Such an otologic picture may be followed abruptly by an intracranial complication. We have histologic sections demonstrating extensive destruction in the petrous pyramid in the presence of a resolving middle ear.

Type 3. The tympanic membrane may be dull gray and somewhat thickened, and some of the landmarks are still visible. While this picture may be associated with signs of mastoiditis and thus resemble type 2 just described (with the exception of the absence of a history of aural discharge at any time), there may be but few symptoms, such as fullness or tinnitus in the ear for a prolonged period. Repeated roentgen examinations are of paramount importance in such instances. That mastoiditis may exist in the absence of aural discharge is well known. We are not concerned here with infants in whom subperiosteal abscess in the absence of aural discharge is not an infrequent finding. An intact drum with involvement of the mastoid is more commonly observed in infections by the pneumococcus type III than in those by the streptococcus.

Type 4. The so-called influenzal type with blebs on the drum and canal requires but little comment. As is well known, the influenza bacillus is seldom found. While the streptococcus is the organism usually recovered, it should be borne in mind that the pneumococcus type III may be the sole invader.

Type 5. It is stated in the literature that the presence of a mucoid aural discharge over a prolonged period is characteristic of pneumococcus type III otitis. We have found this in but 2 instances. In general, the character of the aural discharge does not give one a clue to the type of invading organism.

IMPAIRMENT OF HEARING

Marked impairment of hearing is often present. It was observed in 46 of the 73 cases. Of particular significance is pronounced impairment of

hearing in the presence of an apparently normal tympanic membrane. The drum may be but slightly thickened, the ear dry and the landmarks partly visible; nevertheless, the hearing is impaired to the extent that a forced whisper is not heard. These findings should make one suspicious of *Pneumococcus* type III infection. While marked impairment of hearing is usual, in some instances the hearing may be but little affected. Seven patients with exceptionally good hearing had evidence of mastoiditis, which was verified at operation.

TENDERNESS OVER THE MASTOID

Tenderness over the mastoid is undoubtedly of significance in the diagnosis of postauricular involvement in the majority of cases, as with all other types of infection of the mastoid. It was noted in 49 cases studied. Worthy of mention, however, is the fact that in a fairly considerable number of instances this important sign was absent throughout. Suggestive of the insidious nature of the infection was the occurrence in 7 cases of a subperiosteal abscess, preceded by a more or less symptomless course. It is of importance to emphasize the point that all the patients in this group were in the fifth or the sixth decade.

BACTERIOLOGY

The pneumococcus type III, as is well recognized, is an exceedingly virulent organism, owing to the fact among other things that it is surrounded by a resistant capsule. Biologically the pneumococcus type III differs from the streptococcus in that the virulence of the former does not vary to any appreciable degree as does that of the latter. A characteristic feature of the pneumococcus type III infections of the mastoid is the tendency to gradual but extensive invasion of the contiguous structures. The view generally accepted is that this organism rarely invades the large venous radicles, which may account for the comparative infrequency of sinus thrombophlebitis.

Although the pneumococcus type III is the infecting organism in the middle ear, *Streptococcus haemolyticus* may be recovered from the mastoid. This observation was made in 4 of the cases herein described. Overgrowth of the pneumococcus type III in the mastoid by the streptococcus is the explanation offered for this occurrence. Similarly, cultures of the discharge from the middle ear may repeatedly reveal the presence of *Staphylococcus aureus*. The latter not infrequently overgrows the pneumococcus and thus for a time obscures the bacteriologic diagnosis.

The bacteriologic characteristics of *Pneumococcus* type III just referred to are some of the views expressed by Gregory Schwartzman, bacteriologist at The Mount Sinai Hospital. It is our impression that this organism is frequently dormant in the accessory nasal sinuses and when activated by an acute infection of the respiratory tract may secondarily invade the ear.

In 4 instances an infection of one ear by the pneumococcus type III was followed by an involvement of the other ear by the same organism after a free interval of one and one-half to two years.

ROENTGEN EXAMINATION

In general, we may state that the roentgen findings in themselves are not sufficiently characteristic to warrant a diagnosis of pneumococcus type III infection. In our experience only rarely has the roentgen examination disclosed the "mottled appearance" believed to be suggestive of a destructive process in the bone due to this organism. A roentgenogram showing such a picture, however, has been of inestimable value in establishing the diagnosis of mastoiditis in those cases in which there are few signs or symptoms. Shortly after the diagnosis of pneumococcus type III otitis is made, recourse to repeated roentgen examinations of the mastoid is advisable, in order not to overlook progressive inflammatory changes in the mastoid and petrous pyramid.

OPERATIVE FINDINGS

Before describing the operative findings, reference should be made to the interval between the onset of the aural infection and the appearance of evidence of involvement of the mastoid. The average duration of symptoms (obtained from the history) prior to surgical intervention was thirty-three days. This is a longer interval than is ordinarily observed in streptococcic invasions of the mastoid. Among the cases herein described there was an interval in 1 of five months, in 3 of four months and in 2 of three months.

Mastoidectomy was performed in 69 cases. In a considerable number of these there were no characteristic changes in the bone, the operative findings differing in no way from those of the usual type of mastoiditis. Of importance was the presence in 41 instances of extensive destruction of bone in the mastoid. Marked softening of the bone without actual pus formation was a frequent observation. In addition, a mucoid exudate was occasionally seen. Extensive softening of the bone or a mucoid discharge frequently aroused our suspicion of pneumococcus type III infection, which was subsequently verified by culture. In 23 cases a perisinal abscess was noted, and in 9 an epidural abscess of the middle or posterior fossa. In many instances the destructive processes had extended into the petrous pyramid. Mention was previously made of the rather unusual finding of a subperiosteal abscess in 7 adults.

The postoperative course in the majority of cases observed at the hospital during the past seven years was uneventful. In the decade preceding the period included in the present investigation complications were more commonly encountered. The improvement in the outcome can be ascribed possibly to variations in the virulence of the organism—although, as previously stated, we doubt this—to earlier diagnosis and to more

prompt surgical intervention. An autogenous vaccine recommended by Goldman, Shwartzman and Herschberger (14), was administered to practically all patients in the past seven years.

COMPLICATIONS

In general it can be stated that otitic infections due to the pneumococcus type III are more prone to give rise to intracranial complications than infections of streptococcic origin. Of the complications, meningitis is common. It occurs either early—that is, in the first week of the otitis—or, more commonly, late, after an insidious course with evidence of extensive disease in the temporal bone. Thus, in 4 of our cases meningitis developed during the first week of the otitis and in 8 it occurred much later.

Extension of the inflammatory process to the petrosa is not uncommon. Suppuration in this structure was found in 13 cases, in 8 of which the diagnosis was made clinically. In the remaining 5 there were no physical signs or symptoms the diagnosis having been made by postmortem or histologic examination.

Thrombophlebitis of the sigmoid sinus and jugular bulb, as previously stated, is a comparatively uncommon complication. It occurred in only 3 cases. It is of importance to emphasize the point that the clinical course of sinus thrombophlebitis due to the pneumococcus type III not infrequently is atypical and may be asymptomatic throughout. The diagnosis in such instances is made by recovering the organism from the blood.

Labyrinthitis complicated the otitis in 3 instances; in 2 of these the diagnosis was made clinically and in the third only from histologic sections. Three other patients showed clinical evidence of mild labyrinthine irritation.

Abscess of the temporal lobe was present in 2 instances. Here again this complication occurred as a late development in the prolonged course of the otitis.

Erysipelas was observed in only 2 cases. It is our impression that it is seen much more frequently with streptococcic infections of the ear than with infections due to the organism under discussion. The erysipelas which occurs in the course of pneumococcus type III otitic infections is produced by a secondary invader, the streptococcic organism.

MORTALITY

Of the 73 patients studied, 59 were discharged as improved and 14 died, a mortality rate of 18 per cent. The vast majority of patients were observed for three or four months postoperatively in the outpatient department.

TREATMENT

With full realization of the insidious nature of this infection and its tendency to produce intracranial complications, the necessity for early

diagnosis and thorough surgical intervention must be borne in mind. In cases of suspected pneumococcus type III otitis myringotomy in the early stages is indicated, for the purpose of determining the type of the invading organism. When the bacteriologic diagnosis is established from culture of the exudate from the middle ear a vaccine should be prepared and a series of treatments by intradermal and subcutaneous injection promptly administered, as recommended by Goldman, Shwartzman and Herschberger (14a).

The diagnosis of acute mastoiditis having been made, a mastoidectomy complete in the accepted sense of the word should be performed. In addition to the customary technic of so-called simple mastoidectomy, particular attention must be directed to thorough exenteration of certain areas: the zygoma, solid angle, perilabyrinthine region and any suggestive tract leading into the petrous pyramid. The semicircular canals should be thoroughly skeletonized. The post-auricular wound should be kept wide open, as there is frequently a tendency to rather rapid but superficial healing of the mastoid wound, and during the course of such rapid healing an advancing destructive process may exist in the deeper parts, i.e., the petrous pyramid. Because of the possibility of late complications it is advisable that the patient be observed for about three months after complete healing of the mastoid wound and middle ear. Chemotherapy should be employed during the course of complicating lesions. It is advisable not to use these drugs during an uncomplicated acute middle ear suppuration because of their possible masking effect, particularly as infections of this type are known to frequently follow an insidious course.

PATHOLOGY

Histologic examination of the temporal bone in serial sections was made in 9 cases. The outstanding pathologic feature is extensive necrosis throughout the various structures within the temporal bone, i.e., the mastoid, the petrosa, the labyrinth, the carotid canal and the meningeal coverings. The findings of a resolving inflammatory process in the tympanum and mastoid with evidence of a progressive extension of the disease medially in the petrosa is not infrequent. Confirming a not uncommon operative finding is the observation on histologic examination of an extensive necrotic process with relatively little purulent exudate. It must be mentioned that frequently there are no features differentiating the microscopic picture of this type of infection from that of streptococcal infections.

ABSTRACTS OF CASES

Twenty-one cases are presented in abstract form to illustrate various characteristic and diagnostic features of pneumococcus type III infection described in this paper:

Case 1. A. G., age 29, aroused suspicion of pneumococcus type III infection because of a mucoid discharge from the middle ear at the end of three weeks, a history of headache and slow pulse. The patient had good hearing. There was evidence of involvement of the mastoid. At operation marked necrosis with a small amount of purulent exudate and a perisinal abscess were found. There were meningeal signs. The pneumococcus type III was recovered from fluid obtained by spinal tap seven days postoperatively. The patient died.

Case 2. R. M., aged 66, a diabetic patient, had otitis resembling the influenzal type, but bacteriologic examination of the discharge from the middle ear disclosed the pneumococcus type III. Operation revealed extensive necrosis of the mastoid, encroaching on the petrosa. The patient recovered.

Case 3. S. G., aged 42, had pain in the ear and hemicranium for three weeks but at no time had aural discharge. The drum was flat and thickened, but no landmarks could be seen. There was edema over the mastoid, without tenderness. Hearing was good. Operation showed perforation of the bony cortex. The patient recovered.

Case 4. L. M., aged 56, apparently had influenzal otitis followed by signs of mastoiditis at the end of three weeks. Operation showed extensive destruction with perisinal abscess. Recovery was uneventful.

Case 5. S. P., aged 55, had diabetes and a history of prolonged (two months) aural disease. On admission there were signs of suppurative labyrinthitis and bacterial meningitis (material obtained by lumbar puncture showed the pneumococcus type III).

Case 6. U. P., aged 42, had excellent hearing. Aural discharge ceased after four weeks of otitis. Despite this, frank signs and symptoms of acute mastoiditis were present. Operation showed perisinal and epidural abscess. The patient recovered.

Case 7. A. S., aged 37, showed signs of mastoiditis, and mastoidectomy was performed. Softening extending in all directions made it difficult to reach the limits of disease. Infection by pneumococcus type III was suspected and verified by culture. The patient recovered.

Case 8. S. R., aged 24, had influenzal otitis. Pneumococcus type III was obtained from material obtained by myringotomy. At the end of three weeks there was evidence of mastoiditis. Operation showed extensive destruction of bone. Culture of material from the mastoids showed Str. haemolyticus. The patient recovered.

Case 9. A. K., aged 39, had had otalgia for four months without discharge from the ear. On admission good hearing, signs of mastoiditis and sagging of the bony canal wall were present. Epidural and perisinal abscess were found. Although there was no postoperative clinical evidence of thrombophlebitis, a metastatic focus developed in the sternoclavicular joint, from which the pneumococcus type III was obtained. The patient recovered.

Case 10. H. C., aged 57, was diabetic. The aural disease followed trauma to the ear, and the course was painless for two months, at the end of which time a sub-

periosteal abscess was found over the zygoma, with extensive involvement of the bone over the sinus and dura and little pus. The patient recovered.

Case 11. H. R., aged 50, was diabetic. There had been pain in the ear at the onset, followed by an insidious course for four weeks before spontaneous perforation of the drum occurred. A discharge from the middle ear had been present for ten days. Operation revealed extensive destruction with perisinal abscess. The patient recovered.

Case 12. L. C., aged 45, had had otalgia for two and one-half months without discharge from the middle ear at any time. On admission the hearing was good: zygomatic swelling and sagging of the canal wall were noted. Mastoidectomy was done and zygomatic perforation was found. The Wassermann reaction was 4 plus. The patient recovered.

Case 13. D. G., aged 49, had had otalgia for three days, followed by an interval of five weeks with no pain. Then spontaneous discharge from the middle ear occurred, with recurrence of pain. Sagging of the bony canal wall was observed. Operation showed extensive destruction. Postoperatively there were transient diplopia and pain in the teeth suggestive of petrositis. A roentgenogram was suggestive of petrous involvement. The patient recovered without further operation.

Case 14. A. S., aged 59, had had pain in the right ear for four weeks. The drum was thickened, with radiating blood vessels; there was no discharge from the middle ear. Myringotomy was followed by a thick discharge for one day only and signs of mastoiditis. Operation revealed perforation through the tip of the mastoid and peribulbar abscess. The patient recovered.

Case 15. H. H., aged 59, had had pain and discharge from the ear for two weeks, after which the discharge ceased. Two weeks later postauricular swelling appeared and the bony canal was narrowed. No landmarks were visible, and there was no discharge. Operation revealed perforation through the cortex and perisinal abscess. The bone had a peculiar reddish granular appearance. Syphilis was present. The patient recovered.

Case 16. A. A., aged 40, experienced spontaneous perforation followed by discharge from the middle ear for two weeks. Postauricular swelling appeared at the end of three weeks. Operation revealed subperiosteal and perisinal abscess. The patient recovered.

Case 17. H. Z., aged 40, had had otalgia with a dry middle ear for eleven days. On myringotomy a serous exudate was obtained, culture of which showed *Staph. aureus*. Signs of mastoiditis developed. Operation revealed sclerosis of the mastoid: thick pus appeared under pressure. The pneumococcus type III was cultured from material from the mastoid.

Case 18. C. L., aged 63, was diabetic. Otalgia, ocular pain and temporal headache had been present for one week, followed by spontaneous perforation of the drum. Drowsiness, vomiting and chill were present for four days. There was marked hearing impairment on admission. The discharge from the middle ear was cultured and *Str. haemolyticus* found. Mastoidectomy and obliteration of the sigmoid sinus revealed perisinal abscess, a necrotic sinus wall and a purulent exudate within the lumen. The sigmoid and the lateral sinus were completely thrombosed.

Blood culture showed the pneumococcus type III. The patient died two days postoperatively.

Case 19. L. K., aged 30, had bilateral influenzal otitis media with blebs on the drum. A discharge from the middle ear showed the pneumococcus type III. Signs of mastoiditis developed. The patient refused operation.

Case 20. J. F., aged 64, had had constant tinnitus for sixteen days after swimming and hemicranial pain for two days. There had been no discharge from the middle ear. The drum was thickened, and no landmarks were visible. Post-auricular tenderness was present. Operation revealed a mucoid discharge. The patient recovered.

Case 21. A. I., aged 51, had had tinnitus for four months; he was otherwise symptomless. On admission the drum was thickened, and no landmarks were visible. Sagging of the bony canal was observed. There was no mastoid tenderness. The hearing was impaired. A roentgenogram was suggestive of destruction of bone. Operation revealed extensive destruction and a thin discharge. The patient recovered.

SUMMARY AND CONCLUSION

An analytic study of 73 cases of pneumococcus type III infection of the ear from the standpoint of clinical course, pathology, diagnosis, treatment and outcome is presented.

The cases are classified according to the clinical course and otoscopic picture.

Determination of the type of organism in the discharge from the middle ear or the mastoid is of paramount importance. Such bacteriologic investigation is especially important not only in otitic infections presenting a latent or insidious course but in those which clinically resemble streptococci otitis.

Extensive destruction throughout the temporal bone is a characteristic observation made at operation or on histologic examination. These marked changes are frequently encountered in spite of a latent innocuous clinical course.

Intracranial complications are associated more commonly with otitic infections due to this organism than those due to the streptococcus. They usually occur late in the disease and only occasionally in the early stages.

The following points in the treatment are stressed:

Early paracentesis should be done when infection with the pneumococcus type III is suspected, to establish a diagnosis.

Autogenous vaccine may be used as soon as the organism is identified.

Complete exenteration of all diseased bony structure, with special investigation of various routes into the petrosa is essential. Postoperative evidence of petrositis frequently demands early operative intervention. The recognized surgical procedure should be followed. The administra-

tion of sulfapyridine and of serum should be reserved for otitic complications.

Prolonged observation of the patient after complete healing of the mastoid is of extreme importance.

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PIONEERS IN CARDIOVASCULAR SYPHILIS

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Our knowledge about cardiovascular syphilis has progressed to the point where it is profitable to look back along the path by which it has come and to discern the important milestones that were erected by the pioneer explorers in this territory. Instead of recounting these in the conventional manner it may prove interesting and profitable to go back and examine them as they stand today in the original writings of these great men. The first of the stones are separated by great distances in time but as we approach the present, the markers are much closer together demonstrating the accelerated pace at which progress has been made in recent years.

The only lesion of cardiovascular syphilis about which the ancients knew anything was aneurysm but they had no conception of its true cause. Some thought that those not due to external wounds were caused by the violent throbbing of the spirituous blood within the artery, bursting through its coats from within. It was Ambroise Paré in 1575 who erected the first milestone along the path of our knowledge about cardiovascular syphilis, but on examining it closely it turns out to be only a relatively unimportant one. It had always been my impression that Paré was the first author to give syphilis as one of the causes of aneurysm but when his actual words are studied it seems certain that this is not the fact. Malgaigne (1) in his *Oeuvres Completes D'Ambroise Paré*, published in 1840, gives Paré's statement on this subject as follows:

"Les aneurismes qui viennent aux parties interieures, sont incurables et aduient souvent à ceux qui ont eu la verolle et sué plusieurs fois; à cause que leur sang a esté grandement eschauffé et subtilié, qui est sortis hors, et fait dilatation du corps de l'artire, voire quelquefois à mettre le poing." . . .

"Aneurysms which occur in the inward parts are incurable and occur often in those who have had the pox and sweating several times: as a result of which their blood has been greatly heated and thinned so that what is contained in the arteries tries to get out and causes a dilatation of the artery to the point where sometimes it will contain a fist." This translation seems to show that Ambroise Paré attributed internal aneurysms in syphilitics to the treatment they received and not to the disease itself.

Realizing that Malgaigne's version is a translation from Paré's Latin edition and that it might distort the true meaning let us see how Johnson (2) renders this passage in "The Workes of that famous Chirurgion Am-

brose Parey. Translated out of the Latine and compared with the French" published in London in 1634. "The Aneurismaes which happen in the internall parts are incurable. Such as frequently happen to those who have often had the unction and sweat for the cure of French disease, because the blood being so attenuated and heated therewith that it cannot



FIG. 1. The title page of the First French Edition of "Les Oeuvres" of Ambroise Paré.

be contained in the receptacles of the Artery, it distends it to that largeness as to hold a man's Fist:". You will notice that Johnson says "unction and sweat" indicating even more definitely that it was the treatment that was thought to cause the trouble.

In an attempt to settle the matter let us see what Paré (3) himself said in the first French edition of "Les Oeuvres" published in 1575.

"Les aneurismes qui viennent aux parties interieures, sont incurables, et aduientent souent à ceux qui ont eu la verolle et sué plusieurs fois, à cause que leur sang a esté grandement eschauffé et subtilié qui est cause que celuy qui est contenu aux arteres, cherche à sortir hors, et fait dilatation du corps de lartere, voire quelquesfois à mettre le poing." . . .

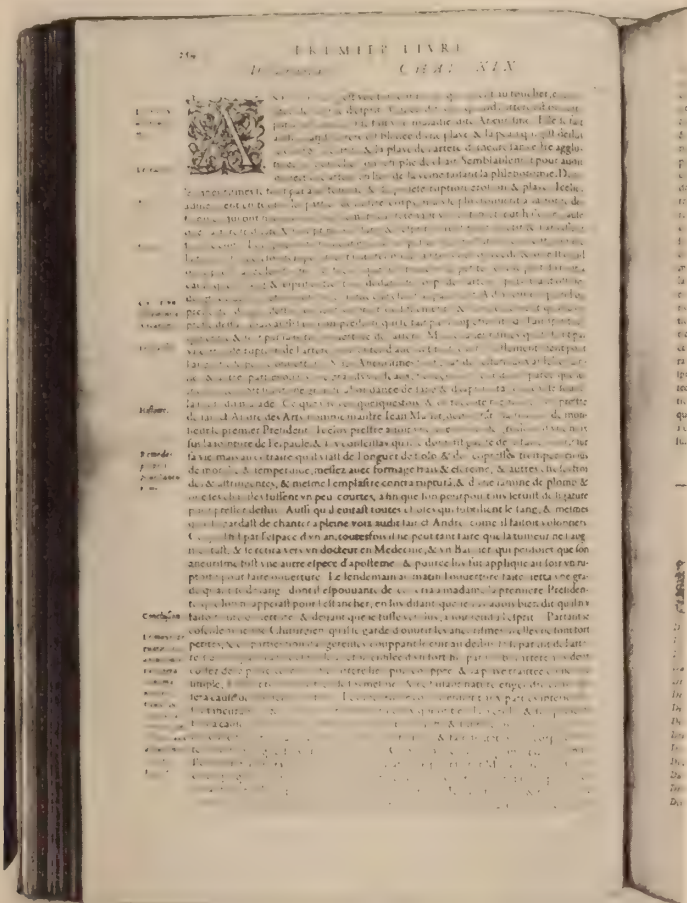


FIG. 2. The page in "Les Oeuvres" where the statement about the cause of aneurysm appears. It begins nine lines from the bottom.

"Aneurysms which appear in the internal parts are incurable and occur often in those who have had the pox and have been sweated several times, as a result of which their blood has been greatly heated and thinned which is the reason why that which is contained in the arteries tries to get out and causes dilatation of the body of the artery, sometimes of a size to contain a fist."

Thus it is clear that Paré noted the frequency of aneurysm in those who

have had syphilis but appears to have attributed the arterial dilatation to sweating used in treatment.

Thus it appears certain that while Ambroise Paré believed the treatment for syphilis and not the disease itself to be the cause of aneurysm in the

JOHANNIS MARIAE LANCISII,
A
 SECRETIORI CUBICULO ET ARCHIATRI
 PONTIFICII,
D E
MOTU CORDIS
E T
ANEURYSMATIBUS
OPUS POSTUMUM,
IN DUAS PARTES DIVISUM
JUXTA EXEMPLAR ROMANUM.



LUGDUNI BATAVORUM,
 Apud { *P. HILIPPUM BONK,*
E T
ANTONIUM GERARDUM STEENMAN. } 1740.

FIG. 3. The title page of Lancisii's—*De Motu Cordis et Aneurysmatibus*. First Edition, 1740.

internal parts, he, nevertheless, was the first man to recognize that there was some connection between syphilis and aneurysm.

The next milestone of importance was erected by Giovanni Maria Lancisii. In his *De Motu cordis et aneurysmatibus* (4) published at Naples in 1740, appears the following:

"Quemadmodum serum acre a cystide et succo aneurysmatico distillans ad ossa, et ligamenta pervadit, eadem paulatim exedit, et tabo consumit, ita ē converso fieri interdum solet, ut lymphæ gallicis salibus scatens postquam congestionem in ossibus, ac ligamentis primo tentaverit, mox paulatim mota acrior jam reddita

ET ANEURYSMATIBUS. 299

PROPOSITIO XXXII.

De modo & causis, quibus fit, & de signis, quibus cognoscitur Aneurysma Gallicum.

Quemadmodum serum acre à cystide & succo Aneurysmatico distillans ad ossa, & ligamenta pervadit, eadem paulatim exedit, & tabo consumit, ita ē converso fieri interdum solet, ut lymphæ gallicis salibus scatens postquam congestionem in ossibus, ac ligamentis primo tentaverit, mox paulatim mota acrior jam reddita supra, & intra substantiam externam Arteriae depluens illam exedere incipiat, indeque in Aneurysma distendat, quod ex compressione simul, & erosione productum tanto reliquis pejus est, quanto minus Medici causæ rationem olim habentes folis sanguinis missionibus, sero, aut lacte plerumque tractare solebant. Cum secus vera curandi methodas tota versetur in temperando idoneis peculiaribus remediis, & ad transpiratum, ac diuresim promovendo veneream lympham, ut inferius appositis exemplis evidenter ostendere satagemus. Hujusmodi liquidum Aneurysmata à venerea cachexia produciuntur, ut optimè advertit Marcus Aurelius Severinus De novissima observatione abscessus pag. mlii 197.

Cognoscitur autem Aneurysma gallicum non solum ex impuro, quod præcessit contagio, atque ex indicis suis venereæ in alias quoque partes jam propagatæ; sed potissimum ex modo, quo determinatus locus Aneurysmate afficitur; Non enim subito Arteriae pulsatio sentitur, sed primo præcurrunt dolores præsertim nocturni alicujus ligamenti, vel ossis; indeque utrumque tumore extuberans subiectam Arteriam premere, atque exedere, ejusdemque pulsationem efficere incipit.

FIG. 4. The page in Lancisii's—*De Motu Cordis et Aneurysmatibus*—in which he gives the first recorded statement that syphilis is a cause of aneurysm.

supra, et intra substantiam externam Arterial depluens illam exedere incipiat, indeque in Aneurysma distendat . . ."

John E. Erichson (5) in his "observations on Aneurysm," published in London in 1844 gives us a very good translation. "As an acrid fluid, distilling from the aneurismal cyst or sac, may penetrate as far as the bones of ligaments, which it may gradually corrode, and wear away; so,

on the contrary, it may sometimes happen that the lymph, abounding in syphilitic humours, may, first of all, give rise to congestion in the bones and ligaments; but by and by, having become more acrid, and settling in the external coat of the artery, it may begin to corrode, and thus to dilate it into an aneurism;..." Thus to Lancisi belongs the credit for the first clear statement that syphilis is a cause of aneurysm.

JO. BAPTISTÆ MORGAGNI

P. P. P. P.

DE SEDIBUS, ET CAUSIS MORBORUM PER ANATOMEN INDAGATIS

LIBRI QUINQUE.

DISSECTIONS, ET ANIMADVERSIONES, NUNC PRIMUM EDITAS,
COMPLECTUNTUR PROPRIUM INNUMERAS, MEDICÆ,
CHIRURGICÆ, ANATOMICIS INCFUTURAS.

Multiplex præfixus est Index rerum, & nominum
accuratissimus.

TOMUS PRIMUS

DUOS PRIORES CONTINENS LIBROS.



VENETIIS,

MDCCLXI.

EX TYPOGRAPHIA REHONDINIANA.
SUPERIORUM PERMISSU, ac PRIVILEGIO.

FIG. 5. The title page of Morgagni's—*De Sedibus, et Causis Morborum*. First Edition. Venice, 1761.

Giovanni Battista Morgagni is the next pioneer who deserves our attention because he gave the first careful description of the pathologic anatomy of an aneurysm. In his *De sedibus et causis morborum* (6) published in 1761 when he was eighty years of age, we read the following,

"Tum eam arteriam ab inferiori extremo, quod ad septum Transversum fuerat, dissecturus, cum vidissem non multo superius, latus eius alterum ad tractum

videbantur, semidiciti intervallo supra eam quae tenet posterioria, erat orificium quod apicem digiti pollicis admisisset, per quod Aorta cum subrotundo aneurysmate communicabat, sacculi forma ad ipsam appensi."

This has been translated for us by Benjamin Alexander (7) in 1769 as follows: "Being then about to lay open that artery from the inferior extremity, which was at the septum transversum, and having seen that one side of it, not much higher, was black to the extent of five or six fingers breath; I found that this was owing merely to the effusion of blood into the cells of the external coat; for the other parts were quite in their natural state. But an internal disease began from the left extremity of the curvature of the aorta, and going from thence quite to the heart, became so much the larger in proportion as the artery came nearer to the heart. That is to say, in some places whitish marks of a future ossification occur'd; in others, some small foramina, as it were, had begun to be form'd, and in still other places were parallel furrows, drawn longitudinally: and in this manner was the surface of the artery unequal here and there. But when I came near to the semilunar valves, which seem'd to be lank and contracted, at the distance of half an inch above that which lies on the back-part, was an orifice that would have admitted the end of a man's thumb by means of which the aorta communicated with a roundish aneurism, that hung to it in the form of a sacculus."

When one remembers that Morgagni was the founder of the science of pathological anatomy one is amazed at the lucidity of his description of the lesions of syphilitic aortitis and aneurysm.

Our next milestone was erected in 1832 by Dominic John Corrigan, physician to the Jervis Street Hospital, Dublin. Here Corrigan devoted himself diligently to the care and treatment of disease and to the study of pathology. In the *Edinburgh Medical and Surgical Journal* (8) in 1832 he published a paper entitled "On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the aortic Valves." In this article he gives the first description of the physical signs of this disease: "1st, visible pulsation of the arteries of the head and superior extremities, 2nd, *Bruit de soufflet* in the ascending aorta, in the carotids, and subclavians, 3rd, *Bruit de soufflet* and fremissiment, or a peculiar rushing thrill felt by the finger, in the carotids and subclavians." Corrigan thinks of patency of the mouth of the aorta as a disease entity, the cause of which is unknown and does not ascribe it to syphilitic infection. Nevertheless, in discussing the diagnosis he has this to say: "The two diseases, aneurism of the aorta, and inadequacy of the valves, may however, be combined. Aneurism of the ascending aorta may, by extending to the mouth of this vessel, dilate it so that the valves are unable to meet, and there is then a combination of the two diseases; there is aneurism and there is permanent patency of the aortic opening." Thus, in 1832, syphilitic aortitis, aortic insufficiency and aneurysm had not been connected as manifestations of the same fundamental pathologic process.

It remained for Philippe Ricord to be the first to describe syphilitic lesions in the myocardium. Ricord was born in Baltimore, United States of America, of French parents and received his preliminary medical educa-

THE
EDINBURGH
MEDICAL AND SURGICAL JOURNAL.

1. APRIL 1832.

PART I.
ORIGINAL COMMUNICATIONS.

ART. I.—*On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves.* By D. J. CORRIGAN, M. D. one of the Physicians to the Charitable Infirmary, Jervis Street, Dublin; Lecturer on the Theory and Practice of Medicine; Consulting Physician to St Patrick's College, Maynooth.—(With Engravings.)

THE disease to which the above name is given has not, so far as I am aware, been described in any of the works on diseases of the heart. The object of the present paper is to supply that deficiency. The disease is not uncommon. It forms a considerable proportion of cases of deranged action of the heart, and it deserves attention from its peculiar signs, its progress, and its treatment. The pathological essence of the disease consists in inefficiency of the valvular apparatus at the mouth of the aorta, in consequence of which the blood sent into the aorta regurgitates into the ventricle. This regurgitation, and the signs by which it is denoted, are not necessarily connected with one particular change of structure in the valvular apparatus, and hence the name *Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves*, has been chosen as simply expressing such a state of the parts as permits the regurgitation to occur.

VOL. XXXVII. NO. III.

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FIG. 7. The first page of Corrigan's article—*On Permanent Patency of the Mouth of the Aorta*. This is the communication in which the pulse of aortic insufficiency is described.

tion in the United States under his eldest brother J. B. Ricord. He went to France in 1820 and soon became interested in venereal disease, eventually becoming the leading authority of his time in this field. In his "Traité

Complet des Maladies Vénériennes" (9) published in 1851 he describes a patient with late syphilis who was under treatment for cutaneous lesions of the shoulder and penis. One day the patient discovered blood flowing from the ulcerating lesion on the penis, felt suddenly very dizzy, lay down on his bed and expired. In the autopsy protocol the heart was described in part as follows:

"... *Les parois ventriculaires présentent, dans plusieurs points, une altération tuberculiforme, constituée par une matière jaunâtre, dure, criant sous la pointe du bistouri, sans vascularité, de consistance squirrhoïde en quelques points et dans d'autres, analogue pour l'aspect à la matière tuberculeuse en voie de ramollissement. En un mot, on retrouva les caractères des nodus ou tubercules syphilitiques, accidents tertiaires qui on observe souvent dans le tissu cellulaire sous-cutané ou sous-muqueux.*" ...



FIG. 8. The gross specimen showing myocardial gummata. Ricord's case, Plate XXIX.

The ventricular walls present at several points a tubercle-like change, consisting of a yellowish material, hard, audible under the point of a bistoury without vascularity, of schirrous consistence at several points and at others similar in appearance to tuberculous material in the process of softening. In a word, one will find there the characteristics of syphilitic nodes or tubercles, tertiary lesions that are often observed in the cellular subcutaneous or submucous tissue." With this observation Ricord set up the next milestone in the path of our knowledge about cardiovascular syphilis. Involvement of the heart muscle by syphilitic lesions was demonstrated.

It remained for Döhle writing in the *Deutsches Archiv für Klinische Medizin* (10) in 1895 to fit the pieces of this puzzle together. He studied patients with syphilis, followed them to autopsy, described the gross and

microscopic lesions he observed in the aorta and came to the following conclusions:

Resultate:

1. Die syphilitische Entzündung der Aorta ist makroskopisch gekennzeichnet durch strahlig-narbige Einziehungen und grubenförmige Vertiefungen der Innenfläche.

Zeitschrift für Hygiene, Bd. L, IV

Tab. VII.

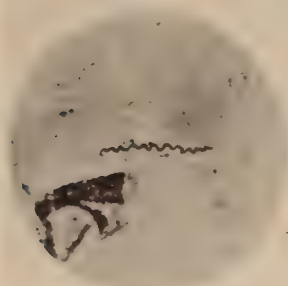


Fig. 9

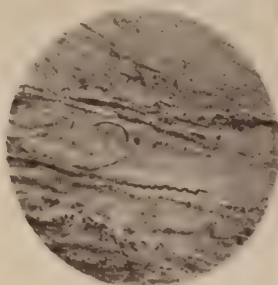


Fig. 10

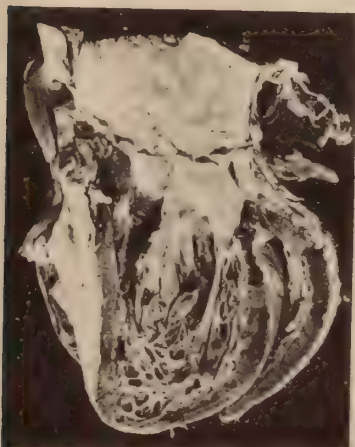


Fig. 11

Von der VIELA COMP. in Leipzig

FIG. 9. The gross specimen and sections in which Reuter first demonstrated the *spirochaete pallida*.

funken der Innenfläche. Daneben kann eine Wucherung der Innenhaut (chronische Endarteriitis) bestehen. Die Einziehungen sind bedingt durch diffuse und gummöse Entzündungen in der Media und Adventitia, die hier zur Entwicklung narbigen Bindegewebes führen.

2. Die entzündlichen Veränderungen der Media ermöglichen die Bildung von Aneurysmen.

1) Syphilitic aortitis is characterized by star shaped scars and depres-

sions of the inner surface. There may be a chronic endarteritis. The contractions are caused by diffuse and gummatous inflammations in the media and adventitia, which lead to scar tissue formation.

- 2) The inflammatory lesions of the media allow the formation of aneurysm.

Before Döhle it was known that aneurysm of the aorta was a syphilitic lesion and its gross pathological anatomy had been well described but to him belongs the credit for the description of syphilitic aortitis and for its recognition as the basic lesion upon which aneurysm develops.

The final proof in the chain of reasoning that connected syphilis and aortitis awaited the work of Karl Reuter. This investigator, only two years after the discovery of the spirochaete pallida by Schaudinn in 1904 demonstrated this organism in the wall of the aorta in a case of syphilitic aortitis. In a paper published in the *Zeitschrift für Hygiene und Infektionskrankheiten* (11) in 1906 appears the following sentence:

"Es fanden sich histologisch zwar keine gummösen Veränderungen, aber doch sämtliche übrigen Kriterien, welche der Hellerschen Aortitis zukommen, in ausgesprochenster Weise, und ausserdem in den nach Levaditis Methode behandelten Stücken der Gefässwand unzweifelhaft zahlreiche Exemplare der Spirochaete pallida."

"Histologically no gummatous changes could be found but all the other criteria of Heller's aortitis were present and above all, in the prepared pieces of tissue of the vessel wall numerous spirochaete pallida were demonstrated by Levaditis method."

Our pioneers Paré, Lancisi, Morgagni, Corrigan, Ricord, Döhle and Reuter have opened up for us the frontiers of cardiovascular syphilis and have left milestones that we may study and in so doing learn the way by which they came. In the beginning their steps were groping and sometimes in the wrong direction but as the path opened up they became more sure. It was they who made the great discoveries in this new field but there still remains much work for men of our time to do before the last frontier has vanished.

The author wishes to express his thanks to Mr. Charles Frankenberger, Librarian of the Medical Society of the County of Kings and to his assistant Mr. Wesley Draper for skillful assistance given in consulting source material. It is noteworthy that all the original publications in their first editions were found in this library except the first edition of *Les Oeuvres* by Ambroise Paré. This is in the Library of the New York Academy of Medicine.

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THE USE OF HIGH FAT AND HIGH PURINE DIETS IN THE DIAGNOSIS OF GOUT

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Acting on the earlier observations (1, 2) that diets high in fat lead to an increase in blood uric acid levels, Lockie and Hubbard (3, 4) in 1935 applied such diets in the study of gouty patients to ascertain their value as a provocative test in the diagnosis of gout. They reported ten trials in five gouty patients and were successful in inducing exacerbations or new attacks in nine of the attempts. In four patients with "chronic arthritis," on the other hand, similar high fat diets were followed by no increase in symptoms. Lockie and Hubbard also observed that the gouty attacks induced by the high fat diet subsided promptly when the diet was changed to one low in fat and protein but high in carbohydrate.

In our own clinic we have long felt the need for an effective provocative test to help establish the diagnosis in doubtful cases. This is especially true in those patients who are first seen when their symptoms are subsiding and in whom, therefore, blood uric acid determinations and the therapeutic test with colchicine often are not informative. For this reason, the study reported here was undertaken to learn whether high fat diets would prove helpful in our hands and to see how they would compare with diets high in purines.

METHOD

Each patient was placed on the ordinary ward diet or on a low purine diet until the acute attack for which he entered the hospital had subsided completely. A high fat diet was then started and continued for a period ranging from seven to twenty-nine days. This was followed by a period of high carbohydrate, low fat and low purine diet lasting three to twelve days. In seven instances an additional period of high purine diet was given for six to fourteen days followed by another trial of high carbohydrate feeding. In one patient still another period of high fat and then of high carbohydrate diet was given (chart 1). The number of grams of carbohydrate, protein and fat in the diets was approximately as follows:

	CARBOHYDRATE	PROTEIN	FAT
High fat.....	50	45	260-300
High carbohydrate.....	300	70	85
High purine.....	119	143	87

The high fat and high carbohydrate diets were low in purines, their protein being derived mainly from milk, eggs and cheese. During the periods of high purine intake the patients received meat at every meal and thymus sweetbreads or liver at least once each day. They also drank 1500 cc. of beer daily.

Uric acid determinations were made by the direct colorimetric method of Benedict (5). For the blood analyses, protein-free filtrates were prepared by Benedict's method (6). Early in the study these were prepared from whole blood but later both whole blood and serum were used and it was found that the figures for the latter were consistently higher than those for whole blood by 0.5 to 1.15 mg. Blood samples were taken twice weekly after breakfast. Twenty-four hour urine collections were made on the corresponding days in some patients.

No drugs which might affect symptoms or uric acid excretion were given except colchicine for the relief of several severe attacks of gout which developed during the periods of study. The diets were tried in gouty subjects and controls as follows:

DISEASE	HIGH FAT DIET		HIGH PURINE DIET	
	Number of trials	Number of patients	Number of trials	Number of patients
Gout—acute	3	2	2	2
Gout—chronic	2	1	0	0
Probable gout	2	2	1	1
Rheumatoid arthritis	2	2	2	2
Normal controls	2	2	2	2

RESULTS

Gout. Two patients (cases 1 and 2 below) had unquestionable gout in the acute stage of the disease, as shown by characteristic histories and joint findings, tophi, and typical response to colchicine, but no deformities or residual joint changes between attacks. Another (case 3A and B) was in the advanced stage of chronic gout with many tophi and severe arthritic deformities. Two other patients (cases 4 and 5) were believed to have gout because of the features noted in the protocols, but were considered questionable for the purposes of this paper because tophi were absent and there was no opportunity to test the therapeutic response to colchicine.

CASE REPORTS

Case 1. History. J. G., a man aged fifty-one was admitted to the Third Medical Division of Bellevue Hospital on October 31, 1936 because of joint pain. The family history was negative for gout and the patient's own story was unremarkable up to 1908 when, at the age of twenty-three, he had joint pain similar to the present attack, which was diagnosed as gout. Two similar attacks occurred about 1912 and then none up to the present, although he had had several hospital admissions because of

acute alcoholism. He was an habitual drinker of beer, taking five to six glasses daily. He had had gonorrheal urethritis in 1928 which had cleared without residua. The present illness began three days before admission with pain, swelling and redness in the left big toe. On the same day the metatarsal region of the left foot and the left knee became similarly involved and the next day both ankles.

Examination. The temperature on admission was 101.8°F. with a corresponding pulse rate. He did not look ill, but obviously was in severe pain. There was no evidence of rheumatic heart disease or urethritis. All teeth were absent. The left knee, both ankles, left metatarsal region and big toes of both feet were painful, tender and warm and presented a purplish-red, swollen, shiny appearance. A tophus present on the right ear was found to contain urates by both microscopic and chemical examination.

Course. The joint symptoms gradually cleared without special therapy and on November 9 a high fat diet was begun. As shown in chart 1, the blood uric acid which had been 4 mg. per cent rose to 6 mg. after five days, but then fell in spite of the fact that the diet was continued unchanged. On November 20 the left big toe became painful, swollen and red, but this too disappeared after two days in spite of continued high fat diet. On November 26 the right ankle and both big toes were similarly involved but once more cleared while the diet remained high in fat. With the change to a high carbohydrate diet, the blood uric acid fell still further to the original level. Following the start of the high purine diet on December 9, the blood uric acid level rose rapidly, but arthritis did not appear until December 21, when the blood uric acid had reached 11 mg. per cent. Both thumbs, the metatarsal regions of both feet and the left big toe were involved and this time pain, swelling and redness were so severe that codeine was required and on December 22 the diet was changed to one high in carbohydrate. Again the blood uric acid fell rapidly but the pain subsided more gradually. On December 29 the high fat diet was resumed. The blood uric acid levels increased only slightly, but on the fifth day acute arthritis reappeared in the left big toe. Once more it subsided after a few days in spite of continuation of the high fat diet.

As is shown in chart 1, the fluctuations in the 24 hour uric acid excretion in the urine tended to parallel those of the blood uric acid level. There is some question about the absolute accuracy of the urine collections between December 15 and December 30.

The patient has attended the arthritis clinic irregularly since discharge and has had two additional admissions to the wards on March 29, 1938 and July 30, 1939, because of arteriosclerotic heart disease with congestive failure and substernal pain. The latter was severe both times, but the presence of myocardial infarction was confirmed electrocardiographically only the second time. During the first of these admissions a typical attack of acute gout occurred on the ward.

Case 2. History. E. M., a fifty-two year old man was admitted on May 6, 1937 in a characteristic attack of acute gout involving the left foot and toes, right ankle and left wrist. He had had these attacks since 1925 and on three previous admissions had shown blood uric acid levels above 7 mg. per cent and typical response to colchicine. There were no tophi and x-ray changes were no more than suggestive of gout. Between attacks the joints were perfectly normal. Serum rather than whole blood was used for the blood uric acid determinations in this patient.

Course. A high fat diet was started on May 15 when the patient was symptom free. The serum uric acid remained about 9 mg. per cent, which it had been before the diet was begun, but on May 22 pain, redness and swelling appeared in the left foot. The regular ward diet was resumed on May 23 but arthritis spread to involve both feet and big toes although the uric acid fell slightly. A high carbohydrate diet

Patient: J.G.
Diagnosis: Gout

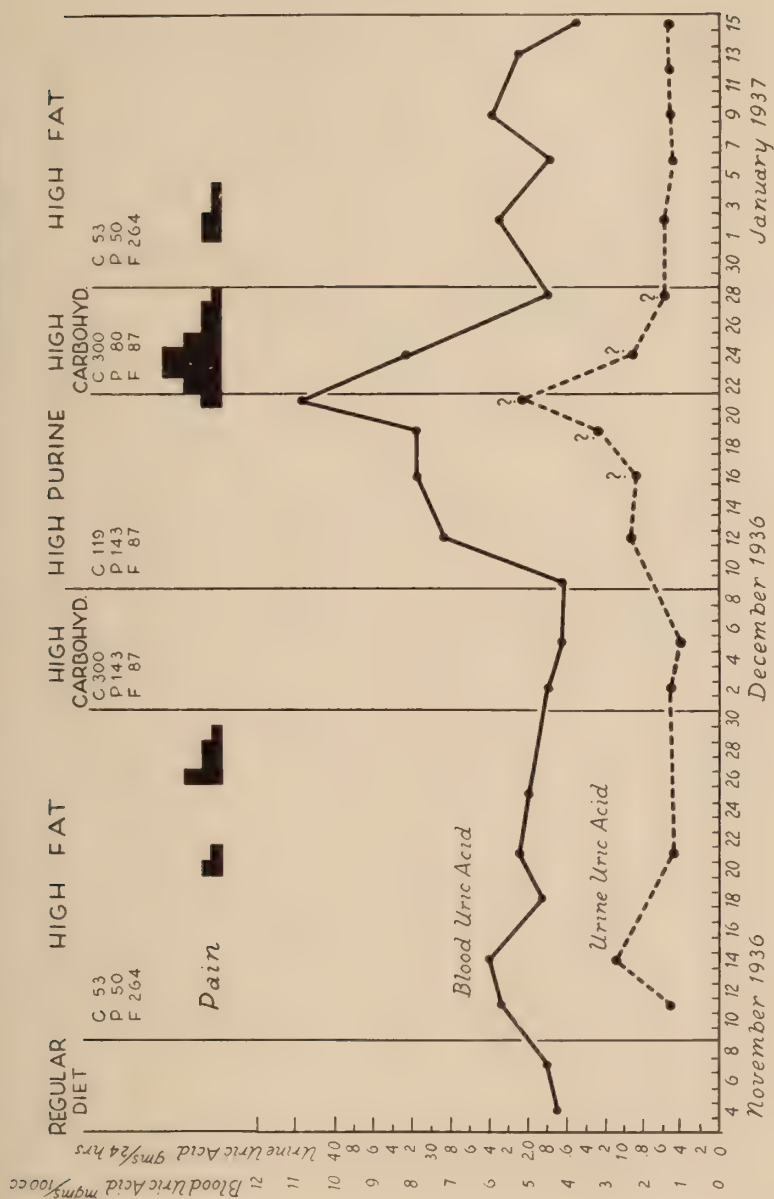


CHART 1

was given from May 27 to June 8 and during that period the patient had no pain and two serum uric acid determinations were 4.7 and 6.6 mg. per cent. With the start of a high purine diet on June 8 the uric acid rose to 11 mg. per cent on June 16. Pain was present in the right big toe on June 15, but it was slight and lasted only one day in spite of continued high purine feeding up to June 21. Since this admission he has had three more attacks of gout.

Case 3A. History. M. K., a man aged fifty-five was admitted on April 30, 1936 in an exacerbation of chronic gout. He had had many attacks since the onset in 1914 but had been entirely normal between attacks up to 1929. Since then there had been progressively increasing deformity and disability which on admission was suggestive of rheumatoid arthritis. The diagnosis was made clear, however, by the presence of numerous tophi which were examined microscopically and chemically.

Course. A high fat diet was started on June 1 when the exacerbation which had brought him to the hospital had subsided. Blood uric acid continued to be between 9 and 10 mg. per cent as it had been on the regular ward diet, but on June 7 pain, swelling and redness appeared in the right elbow and persisted five days. On June 9 the blood uric acid was 10.4 mg. per cent but thereafter it fell gradually to 7.5 mg. per cent on June 18 in spite of continued high fat diet. On that date also pain appeared in the left hip and knee but again cleared after four days although the diet was continued until June 30.

Case 3B. History. The same patient was readmitted January 12, 1937 in another exacerbation. During this admission blood uric acid determinations were made on the serum instead of whole blood. The pain cleared rapidly at first but while still on the regular ward diet a severe attack occurred spontaneously involving wrists, big toes and feet. This subsided on colchicine and a high carbohydrate diet and on February 4 a high fat diet was begun. On admission the serum uric acid had been 7.7 mg. per cent but fell to 5.5 mg. per cent while on regular and high carbohydrate diets. On the high fat regime it rose to 7 and 7.6 mg. per cent on February 6 and February 10 respectively. On February 9 another severe attack of gout occurred in his fingers, right knee and shoulders. Following a change to a high carbohydrate diet on February 12 the uric acid fell sharply to 3.6 mg. per cent by February 17 but then rose to 5 mg. and 7.5 mg. per cent in spite of continued high carbohydrate diet.

Case 4. History. J. B., a man aged forty-eight entered the hospital on October 20, 1936. He had had twelve or more attacks of acute arthritis involving both toes and sometimes the knees, over a period of twenty years. These subsided in seven to ten days and left no residua between attacks. The present one had begun the day before admission. He was a heavy eater of meat and drank much wine and beer. The left big toe and dorsum of the left foot were extremely painful, tender, red, swollen and shiny. There were no tophi and no significant x-ray changes. The blood uric acid on October 21 was 5 mg. per cent. Joint involvement subsided without special therapy and on the regular ward diet the blood uric acid fell to 4 mg. per cent on October 23 and 3.5 mg. per cent on October 26. Following the start of a high fat diet on October 30 the blood uric acid rose to 4.5 mg. per cent on November 3 and 5.8 mg. per cent on November 6 and remained at approximately that level while the diet was maintained. Mild pain appeared in the lumbar region on November 11 which subsided gradually after three days. Following change to high carbohydrate diet on November 13 the blood uric acid fell to 4 mg. per cent on November 17 and remained between 4 and 5 mg. per cent until discharge.

Case 5. History. A. C., a man, aged sixty-two was admitted January 18, 1937 for dietary observation. In 1934 he had experienced his first attack of joint pain in-

volving the right knee and ankle. He stated this had been diagnosed gout. In July 1936 he was admitted to our wards in an acute attack involving the big toes, feet and right knee which subsided spontaneously after five days. The blood uric acid was 6.1 mg. per cent and gout was again diagnosed. There were no tophi or x-ray changes. On January 8, 1937 he experienced a third attack of severe pain, swelling and redness of the metatarsal region of the left foot which cleared save for slight residual soreness after two days. He was consuming large amounts of meat and beer. Serum uric acid determination on admission was 5.4 mg. per cent but fell to 4.5 mg. per cent by February 1. Following the start of a high fat diet on February 2 the serum uric acid level rose to 5.5 mg. per cent on February 4 but then fell steadily to 5 mg. per cent on February 8 and February 11 and 4 mg. per cent on February 15 in spite of a continued high fat diet. On February 14 very slight pain without swelling appeared in the left metatarsal region but disappeared after two days. A high carbohydrate diet from February 20 to February 24 caused no further fall in uric acid. A high purine diet was started on February 24 and the uric acid rose to 7.2 and 7 mg. per cent on February 28 and March 1 and then fell sharply to 3 mg. per cent on March 5 after return to the regular ward diet. There was no joint pain during this period.

Rheumatoid arthritis. Two patients with this type of joint disease were studied in the manner described above. In both patients there were changes in multiple joints typical of rheumatoid arthritis, subcutaneous nodules were present, and the hemolytic streptococcus agglutination reaction was strongly positive.

Case 6. History. L. B., a man, aged fifty-seven was admitted October 12, 1936 with rheumatoid arthritis of two years' duration. Because of continuous low-grade joint pain, acetyl salicylic acid was given throughout the period of study. Uric acid determinations were made on the serum rather than whole blood. A high fat diet was started on April 3, 1937 and the serum uric acid, which had been 4 mg. per cent, rose gradually to 5 and 5.5 mg. per cent on the fourth and fourteenth days respectively but there was no increase in pain above the patient's usual mild level. During seven days of high carbohydrate diet two uric acid determinations gave figures of 4.6 and 5 mg. per cent. Following the start of a high purine diet on April 27 the serum uric acid rose to 10.5 and 11 mg. per cent on May 1 and May 5 respectively. It then fell, however, to 7.8 mg. per cent on May 11 in spite of continued high purine diet. For two days beginning May 4 there was slight increase in the joint pain.

Case 7. History. I. D., a colored woman, aged thirty-three was admitted on January 21, 1938 with rheumatoid arthritis of one year's duration. After the start of high fat diet on February 17, the blood uric acid remained between 2.5 and 3 mg. per cent (as it had been prior to the diet) until March 2 when it reached 4 mg. per cent. High carbohydrate was fed from that date to March 5 when high purine diet was begun. By March 9 the blood uric acid had increased to 5.7 mg. per cent but fell to 5.2 mg. per cent by March 12 on which date the diet was discontinued. Slight exacerbation of pain occurred toward the end of both the high fat and high purine regimes.

Normal controls. Similar observations were carried out on two healthy medical students. In both, the blood uric acid determinations were made on serum rather than whole blood.

Case 8. History. B. S., a normal man, aged 24, began high fat diet on April 6, 1938. On April 8 the serum uric acid was 3.5 mg. per cent as it had been prior to the diet, but it rose to 5 mg. per cent on April 11 and 5.5 mg. per cent on April 15 and then

fell to 4.5 mg. per cent on April 18. High carbohydrate diet was started later that day and the serum uric acid fell still further to 3.9 mg. per cent on April 23. Following high purine diet begun on April 27, the level rose to 5.5 mg. per cent on May 1 and then fell gradually on return to a regular diet. No joint pain occurred.

Case 9. History. P. B., a normal man, aged 27, took the various diets on the same dates as B. S. Prior to the special diets the serum uric acid was 3.6 mg. per cent and this level remained almost constant throughout, rising to only 4.4 and 4.6 mg. per cent on the high fat and high purine diets respectively and falling to only 3.6 mg. per cent on the high carbohydrate regime. There were no joint complaints.

DISCUSSION

From these case reports it can be seen that five trials of high fat diet in patients with unquestionable gout were followed by the appearance of gouty attacks in every instance. This is in agreement with the findings of Lockie and Hubbard (3, 4). However, in their study the new attacks appeared within a few days of the start of the high fat diet whereas in our patients the shortest interval was five days and in one instance eleven days passed before pain occurred. This difference was not due to feeding insufficient fat for the fat content of our diets was higher in most instances than that of the diets used by Lockie and Hubbard. In some of our cases, furthermore, the attacks induced were quite mild and in each instance in which the diet could be continued after the appearance of pain, the attack subsided in spite of the continued diet. Blood uric acid levels increased to some extent in all but two instances (cases 2 and 3A), but in most the increase was slight and several times the levels decreased after a preliminary rise in spite of continuation of the diet. Indeed, in two instances (cases 1 and 3A) the recrudescences of gouty pain occurred while the blood uric acid was falling. Although the number of cases is far too small to warrant drawing a conclusion, the results suggest that the induced attacks were more severe and occurred earlier in the patients with more advanced disease. From the standpoint of diagnosis, the results in the two patients with unproven gout were disappointing, for the slight attacks of joint pain which followed high fat feeding were not entirely convincing (cases 4 and 5). If these two patients have gout, which is probable, it would appear that high fat diets tend to be less informative in those doubtful cases in which help is most needed.

Compared with the high fat diets, the high purine diets led to much more striking increases in blood uric acid. On the other hand, they were not more successful in inducing gouty attacks. Indeed, patient E. M. (case 2) had a much more definite attack on the high fat than on the high purine diet; in the case of J. G. (case 1), however, the reverse was true.

It appears from these results, moreover, that even a marked rise in blood uric acid after high fat or high purine feedings is not diagnostic of gout, for patient L. B. (case 6) with rheumatoid arthritis showed a rise after high

purine diet as marked as that of the patients with gout. This is in general agreement with earlier studies. It seems clear also that either diet to be used as an effective provocative test must be kept up at least two weeks before conclusions can be drawn from a negative response. Like so many other tests, a positive result is much more informative than a negative one. A practical disadvantage of the high fat diet is its unpleasantness. To call the diet unpalatable is gross understatement and many patients would find it impossible to continue it as long as might be necessary.

In chart 1 it will be seen that the 24 hour excretion of uric acid in the urine was recorded as well as the blood uric acid levels for patient J. G. Similar measurements were made in six of the other subjects studied (M. K., J. B., A. C., L. B., B. S., and P. B.). In general the uric acid excretion curves for these patients tended to parallel the fluctuations of the blood uric acid. This was surprising, for other reports (1, 2, 7) of patients during starvation or high fat feeding have shown a diminished excretion, which is thought to be the cause of the increased amount of uric acid in the blood. We have no explanation of this discrepancy between our results and those of others, but are investigating it further.

SUMMARY AND CONCLUSIONS

A study is reported of clinical response and blood uric acid levels of gouty and non-gouty subjects during successive periods of high fat, high carbohydrate and high purine diets. Both high fat and high purine diets led to increased blood uric acid levels but the latter were more effective than the former in this respect. Both diets appeared to be effective in inducing attacks of gout and hence are of value as provocative tests in the diagnosis of that disease. For negative results to be diagnostically significant, however, the diets must be continued at least two weeks. The unpalatable character of the high fat diets is a practical disadvantage. Diets high in carbohydrate and low in fat and purines were followed by a rapid fall in the high blood uric acid and amelioration of the joint symptoms induced by high fat and high purine diets in gouty subjects.

The author wishes to express his thanks to Drs. Philip Berwick, Benjamin I. Schneiderman and Bernard Weisl who assisted in this study as student volunteers.

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EXPERIMENTAL HOLES IN THE RETINA¹

A THEORY OF SPONTANEOUS RETINAL DETACHMENT IN RELATION TO THE ZONULAR MEMBRANE

PRELIMINARY REPORT

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It is well known clinically that in cases of "idiopathic" retinal detachment in which there is an arrow-head or horse-shoe shaped tear, its convexity faces the nerve head, while its concavity is directed forward.

No completely satisfactory explanation of either the shape or position of such a tear has as yet been offered. It occurred to me that the crescentic shape of the tear or hole is caused by the resultant of two forces: 1) a linear pull in the plane of the retina and 2) a push arising from increased pressure in the vitreous.

To check the validity of this idea, tears of the retina were produced in eyes from slaughtered calves and monkeys. The technique finally adopted was to remove an oblong of sclera, and expose the choroid. The eyeball then was held in one hand with a pressure that approximated the intraocular tension present during life. Forceps held in the other hand grasped one point of the choroid. When the choroid was suddenly pulled in its plane an oval hole was produced. The retina was seen to have suffered a simultaneous, smaller, kidney-shaped tear whose concavity was always found to face in the direction of the pull.

In each of four calf eyes a scleral window was made in approximately the same location. In the first eye, a point in the choroid was pulled toward the cornea; in the second toward the optic nerve, in the third to the right, and in the last to the left. All the holes in the retina so produced were kidney-shaped and the concavity faced the respective source of the traction. (fig. 1.)

From these observations it was concluded that in clinical cases of detachment of the retina the arrow-shaped holes are caused by a pull on the retina from a point in front. The only structure capable of exerting such a pull and drawing the retina forward is the ciliary muscle when it contracts. It seems, however, that the structure of the retina is not the

¹ From the Ophthalmological Service of Dr. Kaufman Schlivek, The Mount Sinai Hospital. The author wishes to express his gratitude to Dr. Bernard Samuels whose interest and advice were extremely helpful in the microscopic work, the major part of which was carried out at the New York Eye and Ear Infirmary.

deciding factor in determining the direction of the tear and the relation of its convexity to the optic nerve head.

ANATOMICAL FACTORS

In a preliminary report on the Concept of a Zonular Chamber² the following observations were recorded:

1. *Adherence of the retina to the hyaloid.* After peeling off the sclero-corneal and uveal coats in fresh animal or human eyes, it is seen that the normal adherence of the retina to the underlying hyaloid of the vit-

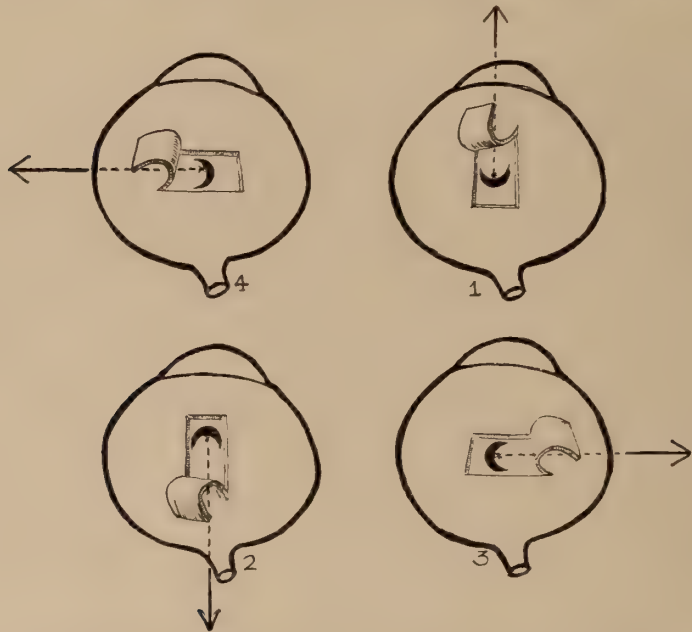


FIG. 1. Schematic drawing showing the four eyes used in one of the experiments. The asterisk indicates the application of the pulling force. The broken arrows show the direction of the pull. The dark crescents represent the resulting tears in the retina. These have the concavity always facing in the direction of the pull, and the convexity away from it. The *operculum* is also shown.

reous is especially marked posterior to the *ora serrata* for about five millimeters.

2. *The hyalo-retinal ligament.* After the retina is removed a whitish line is seen in the hyaloid at the site of the *ora serrata*—the hyalo-retinal ligament.

3. *The hanging vitreous.* When the lens-vitreous is suspended either by a suction bulb applied to the anterior capsule or by sutures taken in the zonular bundles, it is a striking fact that the vitreous still hangs from

²To appear in the Archives of Ophthalmology.

the lens by means of the zonular membrane's insertion into the hyalo-retinal line which thus represents the point of end action of the ciliary muscle.

4. *The zonular chamber.* The microscopic appearance³ of the zonular membrane is re-evaluated in the light of its relatively massive insertion into the gross "hanging" vitreous. Heretofore it was the accepted view that there was a zonular cleft in the hyaloid where the base of the vitreous came in contact with the epithelium of the *pars plana* of the ciliary body. It is my observation made from the study of slides that between the *ora serrata* and the obvious posterior zonular fibres there is a plaque with striations parallel to the choroid. This plaque is separate from the coagulated vitreous strands and forms the hyalo-retinal ligament. This ligament is made up almost entirely of fibrillae from the posterior zonular leaf which is either strung over, or incorporated in, the face of the hyaloid to form with it the posterior boundary of the space existing between the two leaves of the zonular membrane. A communicating band from the anterior leaf helps in its formation. This space may be called the Zonular Chamber.

The proof of the existence of this zonular chamber lies in the fact that it can be injected with carmine in suspension. When the injection is made at any point just beyond the posterior tips of the ciliary processes, the carmine fills this chamber and outlines it as a circular channel, or sinus, which is sharply limited peripherally, or posteriorly, as a wavy line midway between the *ora serrata* and the ciliary processes. From its central, or anterior border this channel communicates with the circumferential space by linear canals running in the valleys of the ciliary body. Almost with the beginning of the injection, the anterior chamber starts to fill up, indicating that there is a free communication either by way of the lesser posterior chamber or Hanover's canal, or both.

Further proof of this concept of the Zonular Chamber is to be seen in slides of pathologic conditions in which serum, blood, exudate, or casts are found confined in this space between the zonular leaves, partially filling it and assuming its shape. In hydrophthalmos the zonular chamber is dilated, and in atrophic globes it is the last recognizable landmark to disappear.

THEORY OF SPONTANEOUS RETINAL DETACHMENT

On the basis of the above anatomic considerations an explanation is offered of detachments of the retina which are not caused by obvious pathological changes or by direct trauma.

³ An interesting contribution for teaching purposes was the development of motion pictures of histology and pathology of the Zonular Chamber demonstrating a continuous, moving microscopic field instead of the usual progressive stills.

A weak spot in the retina caused by sclerosis or by stretching in myopia may become the site of a tear. The hyaloid immediately over it must also be assumed to be defective. Anterior to the weak spot, the hyaloid retains its normal adhesions to the retina. The hyalo-retinal ligament under almost all pathological conditions, continues to maintain its contact with the ciliary epithelium, the *ora serrata*, and the hyaloid peripheral to the *ora*.

In accommodation, the margin of the choroid moves forward with the contraction of the ciliary muscle, and the hyalo-retinal ligament which is in close contact with it, also advances. Because of the relation of the hyalo-retinal ligament to the *ora serrata*, to the hyaloid over the contiguous retina, and to the vitreous, traction on this ligament causes a comparatively increased pressure in the neighboring vitreous. This force is transmitted and disseminated according to the laws of hydrostatic pressure, and affects the posterior wall of the zonular chamber which then becomes compressed.⁴

Mechanism of detachment. When a spasm of the ciliary muscle occurs, the above mentioned results are brought about. At the same time, the increased vitreous pressure on the weak spot in the retina resulting from the overactive accommodation may be augmented by a spasm of the extraocular muscles such as accompanies the sudden increase in tone of the general body musculature occurring in violent physical activity such as sneezing, stumbling, lifting of heavy weights, straining at stools, etc.

The weak spot in the retina when pulled to the front under conditions like the above, may give way and a tear be produced. The concavity faces forward, as seen clinically; and, as I indicated also when produced experimentally. The retina attached to the hyaloid which is connected with the hyalo-retinal ligament, forms the *operculum* and is drawn towards the center of the vitreous. The altered vitreous which is forced through the tear into the subretinal space floats up the retina and so produces the detachment. The push or pressure of the vitreous against the posterior lip of the tear causes the convexity which is directed towards the posterior pole of the eye, as seen ophthalmoscopically.

In the opinion of Dr. Bernard Samuels⁵ even in dialysis or disinsertion of the retina, the tear occurs not at the *ora serrata* but at some distance

⁴ Also, the aqueous present in the zonular chamber is forced into the posterior chamber, ultimately to reach the anterior chamber when the sphincter of the pupil relaxes. It is presumed that the posterior leaf always remains tense, as Tscherning postulated for the hyaloid. The anterior leaf, on the contrary, appears to become first relaxed, according to the Helmholtz theory, and then made taut by the transmission of pressure in the zonular chamber. Therefore, it is felt that while Helmholtz did not go far enough in his theory, Tscherning went too far. The combination of both theories would seem necessary to explain the act of accommodation.

⁵ Personal communication.

from it. This observation is in keeping with the known intimate attachment of the retina to the hyaloid.

If this theory of retinal detachment is correct, practical steps in the operation for its replacement would be to immobilize the ciliary muscle by surface diathermia applied to the sclera, or perhaps to weaken the muscle in the meridian of the tear by cyclodialysis.

DUODENAL ULCER FOLLOWING ACUTE INJURY OF THE SPINAL CORD

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The concept of peptic ulcer as a trophoneurosis gained many new adherents following Cushing's publication (1932) dealing with the relation of peptic ulcers and the interbrain (1). He then proposed the view that irritative disturbances anywhere in the intracranial course of fiber tracts from the anterior hypothalamus to the vagal nuclei in the medulla could be responsible for the production of ulcer. In evidence he cited an extensive literature concerned with this problem for a period of nearly a century and, in confirmation, reported a series of patients dying after operation for brain tumor in whom lesions of the alimentary canal were observed at autopsy. In 7 of these cases the lesions consisted in acute hemorrhagic erosions of the gastric mucosa, acute perforations of the esophagus, stomach, or duodenum, or extensive softening of the lower esophagus and stomach with disruption of the entire wall. In only one case, that of a nine-year-old girl with recurrent cerebellar tumor invading the fourth ventricle, was a pathologically verified chronic ulcer (of the duodenum) observed.

It has been pointed out, however, that most of the evidences of the neurogenic mechanism of ulcer have been based on acute lesions which are fundamentally different from chronic peptic ulcer (2). As in Rokitansky's original description (3) in 1841, these acute lesions, both in man and in experimental animals, vary in size and extent from small superficial hemorrhagic erosions to wide areas of gelatinous and hemorrhagic necrosis with massive rupture. In contrast to ordinary peptic ulcer, these lesions are often multiple, involve the esophagus as well as the stomach and duodenum, and may even involve the mouth (4). They do not follow the usual ulcer distribution along the lesser curvature but appear in widely separated areas of any portion of the wall. They have much in common with Dieulafoy's erosions of the stomach as seen in the severe toxemia of pneumonia (5) or after operation (6), and with Curling's ulcerations of the duodenum in consequence of severe cutaneous burns (7). Such lesions may well have a common basis of pathogenesis in prolonged vasoconstriction affecting the nutrition of the mucosa. This was suggested by Penner and Bernheim (8) in their discussion of ischemic necroses of various tissues occurring in the shock syndrome. In Cushing's own cases the erosive and perfora-

tive lesions were, with one exception, regarded as acute sequelae to the operative procedure upon the brain and not the result of the original tumor. If experimental lesions of the hypothalamus are produced in a manner whereby operative shock and hemorrhage are avoided, significant changes in gastrointestinal activity or secretion do not occur and mucosal changes are not observed at autopsy (Martin and Schnedorf (9)).

These are unquestionably valid objections to the uncritical acceptance of the acute neurogenic erosion as the prototype of chronic peptic ulcer. Nevertheless, the psychosomatic basis of ulcer has become too firmly established in clinical medicine (10) to be overthrown, and the burden of proof is now rather on those who would attempt to disprove it. The chief difficulties at present lie in the elucidation of its mechanism. In contrast to the provocative factors of acute neurogenic erosions and necroses, the factors in ordinary peptic ulcer are probably chronic or recurrent in their action; it is reasonable to assume also that they are comparatively mild, depending upon duration rather than intensity for their ulcerogenic effect. If these assumptions are accepted, the apparent distinctions between acute erosions and chronic peptic ulcer become much less clear-cut or disappear altogether. The question of the distinctive location of chronic ulcer in the *magenstrasse* likewise can be resolved in terms of prolonged opportunity for local factors in the stomach to exert their modifying effect, *e.g.* gastrospasm, pylorospasm, and the action of roughage in the diet.

A number of these questions have been answered successfully in experiments with animals, and an excellent summary of these experiments is available in Cushing's paper. Despite the abundance of this type of proof of the neurogenic theory of true peptic ulcer, unequivocal proofs in human cases are difficult to find. The following case is therefore offered as a fairly clear-cut instance of neurogenic peptic ulcer in which nature provided the experiment in man through the agency of a major accidental injury of the spinal cord.

CASE REPORT

History. Wm. P., a white youth of 16 years, was admitted to St. Peter's Hospital September 1, 1934 as an emergency case. While swimming a short time previously he had dived into shallow water and struck something with his head. He became helpless at once and was brought to the hospital in a state of shock. His past history was negative.

Examination. He had flaccid paralysis of both lower extremities and loss of all sensation below the level of the third rib on each side. Both upper extremities were partly paralysed as well, the chief loss of function being in pronation and supination of the forearms and in gripping with the hands. Sensation was lost in the anterior surface of each arm. No abnormalities were noted in the heart, lungs or abdomen. It was evident that the patient had sustained a serious injury to the spinal cord as a result of fracture of one or more cervical vertebrae.

Roentgenogram of the spine disclosed evidence of a compression fracture of the bodies of the fifth and sixth cervical vertebrae which were angulated posteriorly into

the spinal canal. Treatment consisted in traction to the head and upper cervical spine by means of a collar.

Course. The patient recovered promptly from the initial shock and in four days had recovered some use in his arms and forearms. The paralysis of his lower extremities remained unchanged, however, and there was no return of sensation below the original level of anesthesia (T-III). From the extreme nature of his paralysis and loss of sensation, it was judged that irreversible injury of the spinal cord had taken place and that more radical surgery was unwarranted. No improvement was noted after attempted dehydration therapy by means of concentrated glucose solution (50 per cent) given intravenously.

The patient lived 17 days after admission to the hospital. He was unable to void urine voluntarily and required daily catheterization. Despite methenamine (gr. 22½ daily) and regular bladder irrigation he had continuous pyuria. His temperature ranged between 100° and 103°F., but his pulse remained surprisingly slow (50 to 74).

On the fourth day after injury the patient complained of abdominal pain. The abdomen was somewhat distended and he was, therefore, given an enema. The return appeared normal. On several occasions subsequently he vomited greenish watery material and continued to complain of pain in the abdomen but did not localize it to any particular region. His bowel evacuations were involuntary when he did not receive an enema, and were attended with much flatus. On the twelfth day after injury he complained of severe sore throat. This was found to be caused by the traction collar and a halter was substituted. He began to hiccup and grew irrational at times. On the sixteenth day he seemed slightly improved but still complained of "gas pains"; a rectal tube was inserted and flatus with a small amount of dark brown fluid was expelled. On the following day he refused food, talked irrationally, and seemed unusually drowsy. He evacuated a large amount of black semi-solid stool after an enema and later had an involuntary black watery stool. He was found to be in shock; his pulse had risen to 120, his respirations were labored, and his lips and extremities were cyanosed and cold. Shortly afterward he died.

Necropsy Findings. The subject was well developed and fairly well nourished. Marked pallor was present in the skin and mucous surfaces externally.

Vertebral Column. The centruns of the fifth and sixth cervical vertebrae presented incomplete obliquely vertical fractures which permitted a certain degree of mobility, so that when the vertebral column was extended backward the posterior surface of the centruns together with the intervertebral disc between them were projected backward as a distinct knuckle, compressing the spinal cord. The spinal cord at this point was found reduced to two thirds its normal thickness, and was softened and diffusely brownish in color.

Gastrointestinal Tract. The esophagus appeared normal. The stomach was partly filled with dark brown fluid resembling blood undergoing acid digestion. The mucosa was blood-stained and congested, and covered with some mucus. In the first portion of the duodenum an ulcer was discovered measuring about 15 mm. in diameter. It had clean-cut slightly elevated edges and a flat shaggy base. It was situated on the postero-mesial wall, overlying the head of the pancreas. In the approximate center of the ulcer an open arterial stump was found, projecting upward from the base nearly perpendicularly; its lumen was partly filled with recent blood clot. The deeper portions of this vessel lay more nearly parallel with the base of the ulcer and could be traced into the substance of the subjacent pancreas as one of the smaller branches of the pancreatico-duodenal artery. Its calibre was such as to easily admit a fine probe. The remainder of the small and large intestine was considerably distended with gas and blood, partly fluid, partly clotted, mostly reddish black in color. The appendix contained a rough black pea-size fecalith but was uninfamed.

Thorax. The heart was pale in color and very flabby; both ventricles were somewhat dilated but not hypertrophied. The pericardium, endocardium, coronary vessels and aorta appeared normal. The lungs were somewhat atelectatic and deeply congested in their postero-inferior portions but elsewhere appeared normal. The bronchi contained a moderate amount of frothy mucus.

Liver. Except for pallor, no abnormality was noted in the liver or biliary tract. *Adrenals.* The adrenals were negative. *Pancreas.* The pancreas was negative. *Kidneys.* The kidneys were pale and somewhat soft. Cut section was of normal appearance. The mucosa of the pelves and ureters appeared moderately injected and was covered with thin yellowish purulent exudate. The ureters were flabby and slightly dilated. The bladder was also flabby, and its mucosa was diffusely inflamed, congested, and covered with thin flakes of mucoid pus.

Microscopic Findings. *Duodenum.* Sections through the ulcer showed a sharply abrupt demarcation from the surrounding normal mucosa; the inner sides of the crater were almost vertical, and exhibited a superficial zone of recent necrosis, densely infiltrated with leucocytes and fibrin. There was some overhanging of the edges of the ulcer above the base. The ulcer involved half the thickness of the muscular wall

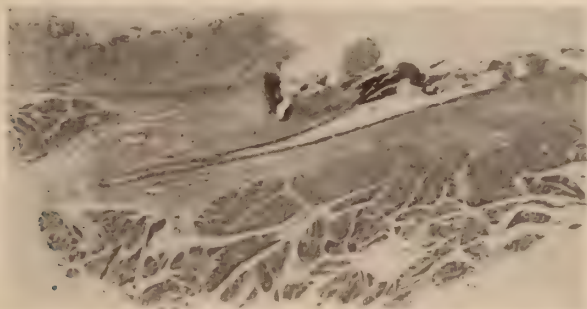


FIG. 1. Section through duodenal ulcer; low power photomicrograph showing eroded artery in base of ulcer from which fatal hemorrhage occurred.

of the duodenum, and its bed was composed of edematous granulation tissue containing numerous young fibroblasts and mononuclear cells, with a superficial infiltration of many polymorphonuclear leucocytes. A fairly large artery was present extending through the entire thickness of the ulcer base which it entered at a marked slant; it appeared normal as far as the ulcer surface at which point its wall had become necrotic and completely eroded over a wide area. Its lumen contained a small amount of partly disintegrated blood clot. The nerve fibers accompanying the artery in its deeper course appeared normal. *Coeliac ganglion.* No abnormalities were noted in the cell bodies or nerve trunks. *Regional lymph nodes.* These exhibited slight edema and inflammatory hyperplasia. *Lungs* (sections from lower lobes): The capillaries of the alveolar septa were greatly distended with blood cells; the alveoli were free of exudate except for slight patchy edema; some atelectasis was also noted. *Myocardium.* The myocardium was negative. The coronary arteries were negative. *Kidney.* The stromal capillaries and the glomeruli appeared contracted and nearly bloodless. *Spleen.* There was irregular congestion of the pulp cords with areas of hemorrhage; the sinusoids, however, appeared contracted and nearly bloodless. *Liver.* The polygonal cells appeared normal except for nearly complete absence of vacuoles. The sinusoids contained little blood.

Diagnosis. Status after fracture dislocation of fifth and sixth cervical vertebrae with severe compression of spinal cord; marked localized softening and atrophy of

spinal cord. Subacute peptic ulcer of duodenum with erosion of branch of pancreaticoduodenal artery resulting in massive hemorrhage. Subacute diffuse cystitis with bilateral acute pyelo-ureteritis. Adynamic ileus. Bilateral slight atonic dilatation of ureters and bladder. Atelectasis and congestion of right lower lobe and left lower lobe of lungs. Anemia of organs. Fecalith of appendix.

COMMENT

The sequence of clinical events and the autopsy findings leave little room for doubt that in this case the duodenal ulcer was causally related to the crushing injury of the cord. The youth of the patient (16 years) and his freedom from previous illness emphasize the role of the injury alone in contrast to the many predisposing factors to ulcer seen in older persons.

The severity of the spinal injury may be judged from the permanence of flaccidity in the paralysed limbs, also from the degree and extent of anesthesia. At autopsy the spinal cord at the level of injury was found to have been reduced to two-thirds its normal thickness and was softened and discolored. Bony compression had been relieved by traction applied soon after the patient was admitted to the hospital, but could be reproduced at autopsy in the form of a sharp buckling when the vertebrae were extended backward. Clinically, anesthesia was complete below T-III, and some impairment of sensation was noted in the arms indicating that only partial interruption of fiber tracts had occurred at the actual level of compression (C-VII).

Despite complete anesthesia below the level of the third rib on each side the patient complained of abdominal pain, presumably the pain of his duodenal ulcer, from the fourth day after his accident until his death from hemorrhage thirteen days later. The presence of ulcer-pain in this patient does not, however, controvert the impression gained from the autopsy that the afferent tracts in the spinal cord had undergone virtually complete interruption. It indicates, rather, that painful sensations were carried, in this case at least, by afferent fibers in the vagus nerves. For many years the question has been debated whether or not afferent impulses are carried by the abdominal fibers of the vagus (11). Recent studies by McSwiney and his collaborators (12, 13) appear to have established beyond dispute that visceral afferent fibers exist in the abdominal branches of the vagus, one group coursing with the main trunk of the vagus directly to the medulla, and another group joining the dorsal roots of the upper thoracic spinal nerves to enter the cord. Failure of the patient to localize his pain to a definite region of the abdomen follows logically from the fact that, since cutaneous sensation in the abdomen had been abolished, reference of visceral pain to somatic segments could not take place (14).

From its nature and location it cannot be doubted either that the spinal injury had caused interruption of all or most of the efferent sympathetic

outflow from higher centers in the brain to the thoraco-lumbar segments of the cord. As an important corollary it may be stated that, inasmuch as the vagi are unaffected by such an injury, removal of the normal sympathetic "counterbalance" leads to a profound vago-sympathetic asynergia with marked vagal dominance. Although studies of the patient's autonomic functions were not made from this standpoint, it should be pointed out that he exhibited persistent bradycardia (50 to 74) throughout his clinical course, even in the presence of fever.

The concept of "vagotonia" has occupied the theorists in the ulcer problem for years (15). Cushing's review of the literature on experimental neurogenic ulcerations led him to conclude that "the peripheral lesions which have led with the greatest constancy in the laboratory to ulcerative lesions have either been paralytic on the part of the sympathetic nerves or stimulatory on the part of the vagus". Consistently successful results have followed sympathetic paralysis by severance of the splanchnic nerves or extirpation of the coeliac plexus (16). Conversely, Keppich (21) in 1921 produced gastric ulcers showing a tendency to chronicity in 10 of 11 rabbits by long continued electrical stimulation of gastric fibers of the vagi. Similar results were obtained in dogs by Stahnke (3) in 1924. Keller (4, 17) produced gastric or duodenal craters in 14 of 29 dogs surviving combined sympathectomy and hypothalamic injury; in these experiments the abdominal sympathetic chains, with or without portions of the thoracic sympathetic chain or the splanchnic nerves were resected bilaterally, and after several days lesions were made in various levels of the hypothalamus. Sympathectomy in itself did not precipitate changes in the gastric mucosa. On the other hand bilateral vagotomy, whether or not combined with hypothalamic injury, failed to produce such craters, but was followed instead by a hemorrhagic change in the gastric mucosa with varying degrees of edema and necrosis; this condition involved practically the whole mucosa. Free acid was present in animals in whom craters formed and was absent in the hemorrhagic state.

While these experimental results emphasize the importance of vago-sympathetic "imbalance" in the causation of ulcer, it should not be inferred that the vagus and the sympathetic have directly opposing functions. As recently stated by Alvarez (18), "the idea of a constant conflict between these two main divisions of the autonomic system does not seem to be supported by experimental observations. Certainly in the case of the digestive tract one can find little sign of antagonism between the vagus and the sympathetic nerves. They both appear to function mainly as restrainers of excessive activity." Indeed, each may complement the other in certain functions, with predominance of vagal activity in the stomach and of sympathetic activity in the colon. There is reason also to believe that most of the so-called inhibitory effect of sympathetic

activity depends merely on reduction in blood flow to organs following vasoconstriction (14). Nevertheless, the two systems are undoubtedly integrated and changes in the functions of one can hardly fail to be reflected in the activity of the other.

From the evidences given previously it is apparent that neurogenic lesions of the upper alimentary tract fall into two contrasting categories, which, for purposes of simplification, may be termed: 1) vagoparalytic and 2) vagostimulatory. In the *vagoparalytic* type, in which the action of the sympathetic mechanism on blood vessels is unopposed, one may expect effects similar to those observed after prolonged vasoconstriction as in various shock syndromes or after prolonged administration of epinephrine. As shown by Penner and Bernheim (8), the anoxemia of the tissues induced by such vasoconstriction leads to edema and hemorrhages and the appearance of tissue necrosis. In this category would naturally fall the acute types of gastromalacia described by Rokitansky (3), Cushing (1), Masten and Bunts (19), and others. In the *vagostimulatory* type, in which vagus activity becomes excessive, either through prolonged overstimulation or through removal of the sympathetic counterbalance, gastric or pyloric hypertonicity and hypersecretion may be expected, culminating in the development of true peptic ulcer. This type would include the ulcers produced experimentally by prolonged administration of acetylcholine (20), prolonged electrical stimulation of the vagi (21), severance of the splanchnic nerves or extirpation of the coeliac plexus (16, 17), and the intraventricular injection of pilocarpine (22). Clinically its counterpart is seen in the observation of continuous oversecretion of acid in patients with peptic ulcer (Winkelstein (23)), and in their reputed hypersensitiveness to the action of pilocarpine (15).

Transecting injury of the cervical cord, therefore, involving interruption of efferent sympathetic pathways, may be said to fulfill the theoretical requirement for the development of neurogenic ulcer on a vagostimulatory basis. Nevertheless, it is difficult to find a counterpart for this case in the literature on peptic ulcer in man. Trophic ulcers of the skin and rapidly developing atrophic changes in bones and joints are well known sequelae to acute lesions of spinal origin (24). In only one case reported in the literature (Polstorff (25)) has gastric ulceration been described in such conditions. In this patient diffuse degenerative disease of the cord in the form of miliary hemorrhages and necroses had developed after violent concussion of the spine from a fall in the course of an epileptic fit. The body of the first lumbar vertebra exhibited an incidental transverse fracture without deformity. Small hemorrhages and focal softening were also discovered in the basal ganglia. In this case death occurred 13 days after the accident and 11 days after the onset of gastric symptoms (vomiting with terminal hematemesis). Four small mucosal defects were found at autopsy along the greater curvature of the stomach, the largest being

lentil-size. According to the author these conformed to the type of acute neurogenic erosion rather than of chronic peptic ulcer.

On the other hand well developed chronic peptic ulcers of the stomach and duodenum have long been known to occur in certain cases of *tabes dorsalis*. Krueg (26) reported two such cases in 1880. Crohn (27) was the first to write on this subject in the American literature. The difficulties in differentiating peptic ulcer from gastric crises in *tabes* have been frequently commented upon (28), and the suggestion has been made that the basis for the pain and occasional hematemesis of gastric crises may well be a mucosal lesion akin to the erosions caused by other types of lesions of the nervous system. In a number of cases perforation was unrecognized until too late because of the similarity of symptoms of peritonitis and of tabetic crisis.

The mechanism of ulcer formation in *tabes dorsalis* is perhaps best explained in terms of vago-sympathetic dissociation of the same general nature as that occurring in the writer's case as well as in the animal experiments described. Other evidences in *tabes* of such dissociation include the frequent finding of postural hypotension, described first by Strisower (29) in 1931 and confirmed in many cases subsequently. This, too, is ascribed to interruption of efferent sympathetic pathways from the brain to the spinal centers (Ellis and Haynes (30)). Depressor effects are more easily obtained than in normal persons, *e.g.* by carotid sinus stimulation, and can be explained by loss of sympathetic counterbalance such as also explains the presumed vagal predominance in those cases of *tabes* having peptic ulcer.

The enormous body of data concerned with psychic factors in ulcerogenesis, rather than conflicting with the principle of vago-sympathetic asynergia, can be considered to complement it, inasmuch as cerebral cortical representation has been shown to exist both for the stimulatory mechanism (31) and for the inhibitory mechanism (32). The probable pathways are from the cortex to the hypothalamus, the red nucleus, the substantia nigra, the centers in the medulla, and the efferent outflows in the vagi and sympathetic nerves. Irritation or paralysis in any part of these pathways may, therefore, affect the condition of the upper alimentary canal, and thereby provoke "trophoneurotic" changes of functional and organic type.

Although the case for vago-sympathetic asynergia in the causation of ulcer is fairly well established by such evidences as those already mentioned, the ultimate mechanism of ulcer formation still awaits elucidation. The concept of trophic disturbance is too indefinite for critical appraisal, and, although perhaps empirically true, may eventually be resolved into one or more of several known mechanisms. Needless to say, neurogenic factors cannot be expected to tell the entire story of peptic ulcer, and, except for occasional cases like the present one, must be considered to have

only subsidiary importance, depending upon the relative importance of such other factors as hormonal balance, nutrition, dietary habits, infection, and heredity.

SUMMARY

A case is presented of typical duodenal ulcer with fatal hemorrhage in a boy of 16 with an acute lesion of the spinal cord. The latter was caused by fracture dislocation of the fifth and sixth cervical vertebrae occurring in a diving accident. The patient complained of abdominal pain for the first time four days after the accident, and it persisted throughout the remainder of his illness. The occurrence of abdominal pain, presumably of ulcer origin, despite the presence of cutaneous anesthesia, is explained by the fact that the vagi, which were unaffected by the injury, contain afferent fibers for visceral sensation. The neurogenic concept of ulcer formation is reviewed briefly, and is analysed in terms of vago-sympathetic asynergia caused either by overstimulation of the vagus or by removal of the normal sympathetic counterbalance. In the present case, as in cases of tabes dorsalis with peptic ulcer, a lesion of the spinal cord involving interruption of sympathetic pathways from the higher centers to the sympathetic ganglia is considered the most likely mechanism of this disturbance.

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THE VALIDITY OF NEPHROSIS AS A NOSOLOGICAL CONCEPT

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Since the introduction of this term into medical nomenclature by Friedrich Müller in 1905 (1), the concept of "nephrosis" has been subjected to so many vicissitudes that today he would not be able to recognize his own offspring. Beginning as an idea, nephrosis has been at various times a unitary pathological lesion, multiple pathological lesions, various clinical syndromes and finally, a single but rare renal lesion with a characteristic clinical expression. No two investigators are agreed as to the strict definition of a nephrosis and the introduction of this term, as with most that have a metaphysical connotation, has created more confusion than otherwise. It is not a disease in the sense that it has a consistent background in pathology. At best, it is a clinical syndrome with multiple morphological backgrounds, not only renal but otherwise. As a consequence of the many adventures that this term has been subject to, one has the right to demand what is meant when this term is employed. Without a definite prefix, "nephrosis" means but very little.

In order to appraise the various evolutions, a brief historical survey is necessary. Müller coined the word "nephrosis" to cover the purely degenerative lesions of the kidney as opposed to the inflammatory. By implication, he referred to the purely parenchymatous or tubular lesions of the kidney, since it was long recognized that these differed clinically from the purely vascular or inflammatory nephritides, edema being the predominant symptom. This attempt at differentiation already involved a number of fallacies. First, because the differentiation was quantitative and not qualitative inasmuch as the inflammatory and vascular nephritides presented tubular changes to a greater or lesser extent and *vice versa*; and second, because to this day the term inflammation has received no precise morphological connotation. "Inflammation" is subject to too many personal interpretations. In fact, Aschoff (2) objected seriously to the term "nephrosis" because to his notion even a degeneration of a cell is an inflammation since it represents a reaction to an injury. In 1913, Munk (3) found in certain patients suffering from what was then diagnosed as "parenchymatous nephritis," with edema as the outstanding symptom, doubly refractile lipid droplets in the urine and on demonstrating that the tubules of such kidneys contained lipid material, introduced the designation "lipoid nephrosis." He regarded the disease as extrarenal, metabolic in mechanism and ascribed active lues as the main

cause. In the meantime, Volhard and Fahr (4) in their classical monograph introduced "nephrosis" as one of the great trinity in their classification of the bilateral hematogenous nephropathies, insuring a foothold for this term that has endured since. Conceiving nephrosis morphologically as any tubular and degenerative lesion of the kidneys, they comprised in their subdivision such diverse lesions as cloudy swelling, fatty and hyaline degeneration, necrosis (mercury poisoning) and amyloid kidney. Since then, other observers have included in their classifications of "nephrosis," the kidney of pregnancy, febrile albuminurias, the kidney in multiple myeloma, the kidney in diabetes and the kidney in jaundice. Volhard and Fahr, however, recognized a clinical entity characterized by tubular degeneration associated with edema and normal renal function which they termed "genuine" or "cryptogenic nephrosis" and which formed an important clinical subgroup. Soon after, came the brilliant investigations of Epstein (5). First, he confirmed the suspicion held by Bright and the actual demonstration by Cstary (6) of a low protein blood content, and of Chauffard and his co-workers (7) who found a high cholesterol blood content in "parenchymatous nephritis" with edema. His outstanding contribution was his application of the neglected law of Starling (8) published in 1896 to the interpretation of the cause of edema. Starling's law is the following: "At any given time there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood in the capillaries for the surrounding fluids. With increased capillary pressure there must be increased transudation—with diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid." Inasmuch as protein exerts a considerable osmotic pressure, any considerable reduction in the total protein of the blood lowers the osmotic pressure to the point when the hydrostatic pressure, especially in the venous end of the capillaries will become dominant and serum will exude into the tissues. The application of this law into clinical medicine has stimulated extensive and fruitful investigations upon blood proteins both in health and disease. Epstein adopted the term "lipoid nephrosis" as the morphological background of the disease which he had previously designated as a "parenchymatous nephritis," the cardinal clinical features of which were the following: marked albuminuria, hypoproteinemia, hypercholesterinemia, double refracting lipoid droplets in the urine, normal systemic arterial tension, secondary anemia, edema or anasarca with a low protein content of the transudate, normal renal function, a lowered basal metabolism and an exceptional tolerance to thyroid preparations. In numerous publications, Epstein has built up a superstructure of theory and pathogenesis which in many particulars has been confirmed.

The concept of "nephrosis" was a direct challenge to pathologists. It did not take long to discover that clinically and morphologically the results

were irreconcilable and that in cases where the clinical mimicry was close, a "lipoid nephrosis" was not always the finding at post-mortem examination but that often a glomerulonephritis, less frequently, an amyloid kidney and rarely, the sclerotic kidney associated with hypertension were found. For the anatomical diagnosis of these cases, the suffix "nephrotic syndrome" was added to differentiate them from the genuine "lipoid nephrosis." Nevertheless, these kidneys aside from the dominant lesion, revealed the characteristic morphological features of the "genuine nephrosis," namely, lipoid deposition of the tubules and the double refractile bodies both in the urine and in the parenchyma. It was correctly concluded that the lipemia represented the underlying pathogenesis responsible for the lipoid deposition in these diverse morphological backgrounds. In the course of further study, it became apparent that many of the clinical features supposedly characteristic of "lipoid nephrosis" notably, edema, low serum protein, hypercholesterinemia and the low protein content of the transudate, occurred in many disorders in which the kidney was not implicated, notably, in protein starvation (war edema), hepatic cirrhosis with repeated tappings, in prolonged slow bleedings from whatever cause, in pernicious anemia, in prolonged ulcerative lesions of the intestines and in certain cases of sprue or sprue-like conditions. The common denominator in these extrarenal maladies is a hypoproteinemia, the result either of loss, deficient intake, failure of formation and in all probability, deficient absorption of protein. Even in these conditions, the suffix "nephrotic syndrome" is often added to the diagnosis, but etymologically, of course, without the slightest justification.

From this brief historical review, it is apparent that the term "nephrosis" has had various nosological interpretations both clinical and morphological. As a consequence, no two current classifications of "nephrosis" agree. We have already quoted Volhard and Fahr's classification. Munk (9) classifies the nephroses thus: 1) albuminous degeneration; 2) fatty degeneration; 3) lipoid degeneration; 4) necrosis; 5) hyaline degeneration; 6) amyloid degeneration; and 7) glycogenic degeneration. Bell (10) classifies the nephroses into two broad groups: (a) the simple nephroses and (b) the special nephroses. Among the simple nephroses he includes 1) those due to chemical poisons; 2) those due to bacterial poisons; and 3) those due to jaundice. Among the special nephroses, he includes 1) the nephrosis of eclampsia and 2) amyloid kidney. "Lipoid nephrosis" is excluded in this classification because he regards it as a glomerulonephritis. Fishberg's (11) classification is the following: 1) Larval nephrosis, under which he includes febrile albuminuria, diabetic nephrosis, the nephrosis of jaundice, hemoglobinemia, Graves' disease and those due to chemical poisons. 2) The necrotizing nephrosis, notably that due to mercury poisoning. 3) Chronic nephrosis which in Fishberg's interpretation is synonymous with "lipoid nephrosis" and 4) amyloid kidney. Finally, Leiter (12) in an

admirable review strictly limits the designation of nephrosis to that conventionally regarded as "lipoid nephrosis" which he regards as suggestive of a primary renal origin. This is a far cry from the original and even transitional designations of this term. Indeed, many clinicians confronted with the maze of conflicting concepts are veering towards Leiter's point of view. The problem narrows down to this. Is "lipoid nephrosis" a biologically pure disease with a consistent etiology, pathology, pathogenesis and clinical expression and course? In order to answer this question a review of some aspects of the current knowledge concerning "lipoid nephrosis" is necessary.

In the first place, the disease known as "lipoid nephrosis" is rare. In The Mount Sinai Hospital, where there has perhaps been more abundant opportunity to observe "lipoid nephrosis" than elsewhere because of Dr. Epstein's association, only one or two cases that meet the strictest criteria may be seen in the course of a year, mostly on the children's service.

Etiology. Since Dieulefoy (13) who in 1899 reported 17 cases of tubular degeneration of the kidney with albuminuria and edema in 17 luetics, mostly in the secondary stage, lues has been a tradition as a cause of "lipoid nephrosis." This tradition received considerable fixation from Munk (9) who in his earliest publication reported the enormous number of 14 cases of "lipoid nephrosis" due to lues. In a more recent edition of his text book (1918), Munk (9) has become somewhat lukewarm in respect to the etiological reaction of lues to "lipoid nephrosis." Reports of most observers give lues a very minor role. It seems to me that this tradition has been founded without sufficient critique. In the first place, a history of lues or a positive serological test in a patient with "lipoid nephrosis" does not necessarily imply cause and effect. Experience is replete with such errors in other branches of medicine and mere associations are not taken into consideration. Second, in many of the reports an albuminuria is the only distinguishing mark of the "nephrosis," diagnosing by inference nothing more than a tubular degeneration. Furthermore, such cases have been reported after the patient has had treatment for his lues, so that it is impossible to assert whether the albuminuria is the result of lues or of treatment. It is true, as Fishberg (11) insists, that neither mercury nor the arsenicals cause sufficient albuminuria to cause edema and that a "lipoid nephrosis" cannot result from treatment alone under any circumstances. The report of a luetic "nephrosis" after treatment has begun is, therefore, manifestly invalid if mere albuminuria is the criterion. In order to ascribe a luetic origin to "lipoid nephrosis" two criteria, it seems to me, are essential. First, that the kidneys at post-mortem examination in syphilitic lipoid nephrosis show either unmistakable lesions of lues or the presence of the spirochete. I have found no instance in which these evidences have been indubitably proven. In fact, in the rare instances of proven luetic involvement of the kidney, a "nephrosis" has not been part

or parcel of the clinical picture. The sponsors of the luetic origin of "lipoid nephrosis" evade this issue by assuming that it is the virus and not the spirochete. Curiously, as far as I can perceive, this is the only instance in all medicine in which the virus of lues has been invoked as the cause of a frankly syphilitic disease. In every other instance, one blames the spirochete. Second, if lues is ascribed as the cause of a "lipoid nephrosis" one should reasonably expect a cure of the "nephrosis" by appropriate treatment, inasmuch as the tubular change is a reversible phenomenon, as evidenced by its occasional curability. I have not been able to find one unmistakable proof in any report that this happened. In one case of apparently typical "lipoid nephrosis" associated with a positive Wassermann reaction which I observed many years ago (in passing, it is the only case in my experience in which lues was suspected), the patient grew steadily worse on antisymphilitic therapy and died of erysipelas following artificial drainage of the leg.

In summary, the causal relation of syphilis to "lipoid nephrosis" must be viewed with much skepticism.

There have been various other causes ascribed to "lipoid nephrosis," notably, infections. I believe the reason for the apparent "cryptogenic" character of "lipoid nephrosis" lies in the fact that "lipoid nephrosis" does not come to observation until long after the initial insult has taken place. "Lipoid nephrosis" like other maladies has a biological course, and the earliest or larval phases we can only surmise, but there is no doubt that a hypoproteinemia, which as we shall see is the dominating agent in the mechanism of "lipoid nephrosis," must persist for a considerable period before the full-fledged picture of "lipoid nephrosis" becomes manifest.

Pathogenesis of "lipoid nephrosis." Epstein's application of Starling's law explains most of the clinical phenomena of "lipoid nephrosis." His contention that hypoproteinemia was the basic factor in the production of the edema and anasarca has received full clinical and experimental confirmation (Landis (14), Gorvaerts (15), Leiter (16)). Furthermore, this mechanism has thrown light upon the hitherto unexplained edemas of extrarenal origin. The critical blood protein level at which edema appears hovers around 5 per cent, *other things being equal*. However, it has since been shown that the osmotic equilibrium of the serum depends more upon the albumin fraction than on either the total protein or globulin content, for the reason that the albumin molecule possesses five times the osmotic pressure of the globulin fraction (Loeb (17)). The determination of the albumin fraction is, therefore, of paramount importance. The critical blood level at which edema appears, again other things being equal, is approximately 2.5 to 3 per cent. The inversion of the albumin-globulin ratio which commonly occurs in "lipoid nephrosis" is due to the smaller albumin molecule as compared to the globulin, whereby far greater quantities of the albumin fraction pass into the urine than globulin. For practical purposes this ratio is not important.

There is but little question that the hypoproteinemia of "lipoid nephrosis" is the result of loss of albumin by way of the urine. The loss may be great, even 25 to 30 grams a day. Considering that the total plasma albumin of a man weighing 70 kilos is 140 grams, the drain unless compensated by regeneration is enormous. How much protein may be lost in the urine daily in order to cause hypoproteinemia cannot be answered with any precision because the time factor must be considered. Patients who pass only traces of protein are never in danger of developing hypoproteinemia. To what extent the protein loss occurs by way of the glomeruli or tubules is debatable, and for the interpretation of "lipoid nephritis" a matter of indifference. At one time, Epstein sponsored the theory that "lipoid nephrosis" was primarily the result of biologically altered serum protein but this is hardly tenable in view of the fact that a clinical picture identical with that of "lipoid nephrosis" may be caused by a glomerulonephritis and other renal lesions in which the assumption of altered serum protein cannot be considered. Furthermore, it renders the not infrequent cure of "lipoid nephrosis," by diet and thyroid and even spontaneously, difficult to understand. Indeed, most observers have found the serum and urinary proteins to be identical. On the other hand, Goettsch and Lyttle (18) recently have reported abnormal albumins and globulins in the serum of nephrotic patients. If confirmed, it still remains to be shown whether this change is primary or secondary.

Hypoproteinemia is not an exclusive feature of "lipoid nephrosis" but part and parcel of a host of other maladies, renal and otherwise. First, it is found in any renal disorder in which a considerable proteinuria is a feature; in glomerulonephritis very commonly; less frequently in amyloidosis and rarely in nephrosclerosis with hypertension. These observations alone negate a metabolic disorder and substantiate a primary renal origin in "lipoid nephrosis." Second, and perhaps more significant, are the hypoproteinemias of extrarenal origin. Some years ago (19), I summarized these disorders under three headings. 1) Those due to loss of protein. In this group belong the renal diseases just mentioned; anasarca of whatever origin, hepatic or cardiac, in whom repeated tapplings are necessary; prolonged and repeated hemorrhages, for instance, from a peptic ulcer; and dysenteries in which much serum and blood are lost in the stools. 2) Deficient intake of protein. This occurs in "war edema" and starvation and is especially common in the tropics as the result of an inadequate protein diet; also in chronic alcoholism and in the protein deficiency of horses. 3) Insufficient formation of protein. This occurs in pernicious anemia; in severe disease of the liver and as a secondary factor in "nephrotic states." To this classification I would now add 4) failure of protein absorption. This accounts for the hypoproteinemia occasionally seen in sprue. The final proof of the sequential relation between hypoproteinemia and edema was demonstrated by Leiter (16) by plasmaphoresis. It must be remembered that while hypoproteinemia is the main conditioning factor

in producing the edema of "lipoid nephrosis," the edema is to a certain extent modified and controllable by electrolytes, especially the sodium ion. Furthermore, all hypoproteinemias of whatever origin, clinical and experimental, have another attribute in common with "lipoid nephrosis," namely, the low protein content of the edematous transudate, quantitatively proportionate to that found by Epstein in edema of "lipoid nephrosis." This observation incidentally renders highly improbable a mechanism once seriously held, that increased permeability or damage of the capillaries was the cause of the edema in "lipoid nephrosis."

Hypoproteinemia does not limit its sphere of influence in merely creating edema. There is hardly any question but that it bears some relation to the development of the lipemia that is so consistently present in "lipoid nephrosis." The relation is probably an indirect one and as yet, not clearly understood.

In many of the earliest investigations, the lipemia was viewed as secondary to the primary deposit of lipid in the kidney, thus again suggesting that "lipoid nephrosis" is a metabolic disease, but this view is no longer tenable in view of the fact that a lipemia is just as consistently present in hypoproteinemias of extrarenal origin. Although there is no direct quantitative relation, a lipemia occurs in practically every disease associated with a hypoproteinemia and even experimentally by bleeding (Fishberg and Fishberg (20)), by plasmaphoresis (Leiter (16), Barker and Kirk (21), and by experimental protein inanition (Weech and Ling (22)). Certain explanations have been proposed for this remarkable correlation; that the lipemia helps to neutralize the lowered osmotic tension (20); that as the result of the protein depletion there is a mobilization of fat from other depots (23) similar to that found in certain cachectic states; that it is the result of the associated anemia. That lipemia does not represent a primary disturbance in metabolism is proven by the observations, first, that it follows and does not precede a hypoproteinemia and second, that in other states associated with lipemia, for instance, xanthomatosis, a lesion even remotely resembling "lipoid nephrosis" is never produced.

It seems to me that the best explanation of the lipemia in "lipoid nephrosis" lies in its relation to the lowered basal metabolism so uniformly found in hypoproteinemic states. The lowered basal metabolism in "lipoid nephrosis" was viewed by Epstein as supporting his conception that it is a metabolic disease, and the familiar tolerance such patients possess for thyroid medication seemed to support his contention. He admitted that the differentiation between "lipoid nephrosis" and myxedema was sometimes difficult; indeed, the association of the two has been reported.

In a recent paper (24), I submitted abundant evidence that the lowered basal metabolism in "nephrotic states" could only be explained by the edema which acting as a suit of clothes, prevented the dissipation of heat from the body. Indeed, I showed that any malady associated with in-

tegumentary thickening was often accompanied by a lowered basal metabolism, for instance, ichthyosis, the edematous stage of scleroderma, certain cases of congestive failure without active dyspnea or tachycardia and true myxedema. It is a remarkable fact that in all the above mentioned conditions a lipemia as represented by a hypercholestrinemia was invariably present. These observations afford additional evidence that the lipemia in "lipoid nephrosis" is not a primary disturbance in metabolism. The genesis of lipemia in "lipoid nephrosis" may be represented in the following mechanism: hypoproteinemia \rightarrow edema \rightarrow lowered basal metabolism \rightarrow lipemia (hypercholestrinemia). At the same time, these evidences disprove the one time assumption that the lowered basal metabolism in "lipoid nephrosis" is entirely the result of an associated primary hypothyroidism. More likely, the lowered metabolic rate in edematous conditions is at the expense of the extra-thyroid moiety of the total metabolism; and whatever effect the administration of thyroid preparations in "lipoid nephrosis" may possess, the result is symptomatic and not specific. The lipemia accompanying lowered metabolic states has all the earmarks of a compensatory phenomenon but the precise teleology is entirely unknown, and will remain so until the function of the steroids in body economy is better understood.

In this rather cursory summary, we have seen that most of the cardinal clinical evidences, namely, hypoproteinemia, edema, low protein content of the transudate, lipemia, lowered basal metabolism and the low osmotic pressure of the blood are by no means the exclusive property of "lipoid nephrosis" but occur in manifold maladies, renal and otherwise, the essential linkage being a hypoproteinemia. The issue that now confronts us is what additional property or properties does "lipoid nephrosis" possess that confers upon it the dignity of a nosological entity? We may exclude the extrarenal disorders at once because they do not enter into the differential conflict and shall limit ourselves to the renal disorders that simulate "lipoid nephrosis."

First, the differentiation is based on clinical grounds. The differentiation of "lipoid nephrosis" from amyloid disease and nephrosclerosis with hypertension affords little or no difficulty. The malady from which "lipoid nephrosis" more often meets difficulty in differentiation is glomerulonephritis. Those who uphold "lipoid nephrosis" as a disease entity contend that glomerulonephritis differs from "lipoid nephrosis" in three essentials; first, the cause of "lipoid nephrosis" is unknown; second, "lipoid nephrosis" is not associated with hypertension and third, renal function is not impaired in "lipoid nephrosis." Let us view these differentials closely.

The factor as to whether the cause of a disease is known or unknown cannot be reasonably employed as a measure of differentiation. We have already discussed one of the reasons why the cause of "lipoid nephrosis" is unknown, namely, that the patient only comes to observation long after

the initial insult. The opportunity to observe the biology of the disease from its very inception is most desirable. Furthermore, although the probability is strong that an infection, usually the streptococcus, initiates a glomerulonephritis (the mechanism is still not clear), in the vast majority of instances especially of the chronic type, the cause is not obtainable, at least, in our experience. However, this is no bar to the diagnosis. The question of elevation of blood pressure is important for the differentiation between "lipoid nephrosis" and glomerulonephritis, *provided it is present*. Whether hypertension may be absent throughout the *entire* course of a proven glomerulonephritis is questionable but that it is absent at some particular cross section of the life cycle is a familiar observation. I have repeatedly witnessed the disappearance of hypertension in the subacute or chronic stage of a glomerulonephritis. Had the presence of hypertension escaped us, the diagnosis of "lipoid nephrosis" in those who presented a "nephrotic syndrome" would have been perfectly justified. The absence of renal insufficiency in "lipoid nephrosis" would also be a justifiable differentiation from glomerulonephritis provided that renal insufficiency is an invariable accompaniment of glomerulonephritis, but it is well known that the milder types of chronic glomerulonephritis may persist for many years without any evidence of impairment of renal function.

In the last analysis, therefore, these clinical differentials are entirely arbitrary, and do not take into consideration the possible biology of the disease.

Pathology. Finally, the standing of "lipoid nephrosis" as a disease has been based on a distinctive morphology. It is admitted that the deposition of lipid, mostly doubly refractile, in the epithelial cells of the tubules and to a certain extent in the glomeruli and interstitium, is not the specific lesion of lipoid nephrosis inasmuch as this deposition is also found in glomerulonephritis and amyloid kidney with a "nephrotic" tendency. The specificity of the lesion of "lipoid nephrosis" is supposed to depend not only upon the comparative integrity of the glomeruli but also *upon the absence of morphological changes conventionally recognized as those of a glomerulonephritis*. In view of the striking clinical mimicry between the two diseases, many distinguished pathologists have suspected that "lipoid nephrosis" is the result of a glomerulonephritis and much controversy has raged upon the interpretation of glomerular changes that have been observed in "lipoid nephrosis." There is no need to review the pros and cons of these debates; the conclusion is invariably reached that the minimal glomerular lesions in "lipoid nephrosis" are not comparable to those found in the ordinary types of glomerulonephritis. The matter remained dormant until recently when Bell (25) revived the controversy. Employing a histological technique of MacGregor, Bell described in four cases of what he believed to be "lipoid nephrosis" a thickening of the basement capillary membrane and a varying increase in the number and size of the glomerular

endothelium lesions which he interpreted as a glomerulonephritis. Bell's conclusions have been criticized, for instance, by Leiter (16) on the ground that none of his four cases appeared to be unalloyed instances of pure "lipoid nephrosis" clinically. In all probability they were cases of glomerulonephritis with a "nephrotic component." Kantrowitz and Klemperer (26) with the same technique found no semblance of a glomerulonephritis in undoubted "lipoid nephrosis."

The matter does not rest here. Because the kidneys do not show the conventional histological lesions of glomerulonephritis does not necessarily imply that *such lesions may not previously have existed*. The entire problem hangs upon whether our knowledge of the morphological evolution of the lesions of acute glomerulonephritis is complete. This is far from being the case. 1) We are well informed of this evolution in clinically progressive chronic glomerulonephritis whether associated with a nephrotic component or otherwise, but we are still entirely unacquainted with the morphological appearance of the glomeruli in clinically healed cases. Being largely a productive inflammation with proliferation of the intra- and extra-capillary endothelium of the glomeruli as the predominant lesion, some have presumed that complete restoration to the normal is never completely attained. This question still awaits solution. After a diligent quest extending over many years, I have not been able to find such a kidney. 2) We now come to the crux of the problem. For years, clinicians have observed that occasionally clinically established cases of acute glomerulonephritis lose their hypertension, renal insufficiency, etc. and eventually develop the typical clinical picture and course of "lipoid nephrosis." At times, even complete recovery ensues. While such observations are not common I have observed perhaps half a dozen in the course of the past twenty-five years. What glomerular lesions may we expect to find in such an instance? The only case that satisfies the above mentioned clinical requirements and that has come to post-mortem examination at The Mount Sinai Hospital is the following, a complete report of which will be shortly published by Drs. Jerome Kohn and Herman Schwarz of the Pediatric Service. Furthermore, this case presented the first opportunity to study the development of a "lipoid nephrosis" from its very inception to its terminal phase.

CASE REPORT

History (Adm. 461645). R. H., age 3 years, was first admitted December 3, 1939. The child had been sick with fever and sore throat for a week, swelling of face and abdomen for two days, and red urine for one day. There was moderate swelling of face and legs. The temperature was 103°F., but returned to normal the next day. There was evidence of receding tonsillitis. The blood pressure was 140 systolic and 100 diastolic; the blood urea nitrogen was 8 mg. per 100 cc.; the serum protein was 5.1 per cent of which the albumin fraction was 3.8 per cent. The urine contained albumin 2 plus, red blood cells and a few casts. On December 5, it was noted there was no gross blood in the urine. On discharge, December 19, 1939, albumin had disappeared from the urine. On February 1, 1930, in the follow-up clinic, the pa-

tient gave a history of having had "grippe" two weeks before. Moderate edema was noted over the tibia, the urine contained albumin 2 plus, the blood pressure was 120 systolic and 80 diastolic.

Second admission (March 12, 1940). Three weeks before admission generalized edema was noted. The blood pressure was 124 systolic and 90 diastolic: the blood urea nitrogen 9 mg. per 100 cc.; the total serum protein 4.5 per cent of which the albumin fraction was 2.5 per cent; and the cholesterol 550 mg. per 100 cc. The child was placed on a high protein diet and given 8 grains of thyroid without effect. During her stay in the hospital the edema persisted, the urinary albumin was 3 plus. the cholesterol was high, on one occasion attaining 1050 mg. per 100 cc. The blood pressure remained about the same. There was one attack of abdominal pain with fever. The patient was discharged August 6, 1940.

Third admission (August 25, 1941). No clinical improvement was noted during her home stay. The blood pressure was 110 systolic and 85 diastolic. The serum protein was 3.3 per cent of which the albumin fraction was 1.5 per cent. The blood chemistry was the same as on the last admission. The child had erysipelas twice. The child died of a pneumococcus peritonitis on January 12, 1941. (The urine always contained 4 plus albumin with a few red blood cells and rare casts.) Two weeks before death the blood urea nitrogen was 28 mg. per 100 cc.

Necropsy findings (P.M. 11728). The renal architecture of the *kidney* seems not to be profoundly disturbed; however, throughout the cortex one sees small foci of tubular atrophy with increased stroma and frequently one sees the stroma widened with infiltration by lymphocytes with occasional polymorphonuclear leucocytes. The first convoluted tubules are quite distended and contain a considerable amount of albumin. The epithelial cells generally show a good brush border and the cytoplasm is finely granular. The terminal portion of the convoluted tubules contains a large amount of pink granular material which is probably albumin. The epithelium in such portions shows vacuolization. *Glomeruli*: A superficial examination of the glomeruli seem to indicate that they are not materially altered. However, if one examines more carefully, one finds certain changes effecting the majority of the glomeruli. The lobulation of the tuft is exaggerated and the lobules appear rather plump. The basement membrane of the capillary loops are quite thick and there is fusion of such loops with each other and with the capsule. Some glomeruli show multiplication of the capsule epithelium. The Bowman's space contains only a small amount of albumin.

The two kidneys together weighed 240 grams. They were enlarged, white-yellow and soft. The capsule stripped with ease. There is no scarring, hemorrhages or granularity of the surface. On section, the cortex and medulla are sharply demarcated. The glomeruli are visualized as pin-point red dots.

COMMENT

It is apparent that the changes in the glomeruli that are not completely intact correspond closely to those described by Fahr (27), Munk (9) and others in "lipoid nephrosis," even in regard to their focal distribution. In addition, there was thickening of the basement membrane as described by Bell (26). The histological changes of the previous glomerulonephritis have almost completely resolved except for a minimal proliferation of the capillary endothelium, thickening of the basement membrane and occasional fusion of the glomerular loops. In other words, this kidney might be regarded morphologically as characteristic of "lipoid nephrosis" *provided*

we were not aware that the patient had previously passed through a well established acute glomerulonephritis. In other words, we have witnessed in this case the evolution, both clinical and morphological, of acute glomerulonephritis to "lipoid nephrosis." Had this patient been seen for the first time during the third admission, the diagnosis of "lipoid nephrosis" would have been, according to present criteria, perfectly correct which again substantiates our conclusion that the majority of patients with clinical "lipoid nephrosis" come to observation only after the initial phases have passed. In short, a correct interpretation of "lipoid nephrosis" requires a complete survey of the biology of the disease, both clinical and anatomical.

Obviously, we are in no position to assume that a glomerulonephritis is always the basic pathology of clinical "lipoid nephrosis" but the possibility is strong that this sequence is exceedingly common. This would account in a measure at least, for the rarely reported instances of "nephrotic contracted kidney." That glomerulonephritis cannot account for all the cases of "lipoid nephrosis" is instanced by a case of bilateral thrombosis of the renal veins with a complete clinical picture of "lipoid nephrosis" that was observed at The Mount Sinai Hospital a few years ago.

On all *a priori* grounds, as we have tried to convey in our discussion of the pathogenesis, a primary renal origin of "lipoid nephrosis" is almost an inevitable conclusion. Nevertheless, clinical "lipoid nephrosis" is by no means synonymous with anatomical "lipoid nephrosis."

SUMMARY

Historically, the term "nephrosis" has meant many things; a non-inflammatory and degenerative renal lesion, an arbitrarily defined clinical concept, a syndrome associated with multiple backgrounds in pathology both renal and otherwise and finally, a delimited disease with a single background in pathology designated as "lipoid nephrosis." The fundamental characteristic clinical phenomena of "nephrosis" are reviewed and their pathogenesis outlined. The primary factor is a hypoproteinemia which may be the result of loss, deficient intake, insufficient formation and poor absorption of protein. The hypoproteinemia is responsible for the edema and anasarca and for the low protein content of the exudate. In addition, the hypoproteinemia is indirectly responsible for the low basal metabolism by creating an edema which acts as a suit of clothes preventing the dissipation of heat. This is in conformity with the observation that all integumentary thickenings are usually accompanied by a low basal metabolism. The lipemia of "nephrosis" represents, in all probability, a compensatory phenomenon for the low metabolism, inasmuch as a lipemia is also the usual accompaniment of many edematous states and of integumentary thickenings. The validity of "lipoid nephrosis" as a distinct disease entity depends on whether it possesses a precise background clinically and mor-

phologically. Clinically, "lipoid nephrosis" can be differentiated from conditions that simulate it only by arbitrary criteria. Anatomically, "lipoid nephrosis" has no specific or consistent background. There is evidence that in certain instances the lesion of "lipoid nephrosis" represents a glomerulonephritis in which almost complete resolution has occurred. Clinical and anatomical "lipoid nephroses" are by no means synonymous. In the last analysis, "nephrosis" is not a disease and requires precise definition when the term is employed.

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PUTRID EMPYEMA WITHOUT FETID SPUTUM ("SURPRISE" EMPYEMA)

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A case observed and treated jointly with B. S. Oppenheimer gives point to the observation, made upon a number of occasions, that not only putrid pulmonary abscess but also putrid empyema may exist in the absence of fetid sputum. Foul pus encountered in such cases either at exploratory puncture or at operation is usually unexpected and decidedly in the nature of a surprise. Instances have been seen in sufficient numbers to warrant the statement that they comprise an important variant of the putrid pulmonopleural infections requiring special consideration from the viewpoint of diagnosis and therapy. There are two reasons for describing the following case observed in conjunction with B. S. Oppenheimer: it serves as a striking example of the lesion in question, and it illustrates the thoughtful and painstaking study B. S. Oppenheimer is wont to make when atypical features are present in any case. The preadmission notes are chiefly transcripts from his own annotations on the patient's chart:

History (Adm. 431928). Mrs. A. R., 46 years old, was admitted to The Mount Sinai Hospital on November 7, 1938, with the history of a "cold" beginning about October 2. For three weeks there had been slight cough, vague pain in the back, and scanty expectoration. On October 23 there began, with abrupt onset, violent pain in the left chest radiating to the back and left shoulder. This persisted with unabated violence for two days in which period of time there was no fever. Thereafter the pain subsided. Fever began on October 25 and ranged between 102° to 104°F. throughout the preadmission period. Cough was persistent, but remained essentially unproductive until shortly before admission. A roentgenogram on October 25, two days after the onset of pain, indicated the existence of consolidation and fluid over the left lower lobe. On November 7 the white blood count was 22,800, with 85 per cent of polymorphonuclear leucocytes.

Shortly before admission, Mrs. A. R.'s general condition became worse rather suddenly. The following note is transcribed: Constant cough, no fetor. Whitish sputum. Clubbing of finger tips. Cyanosis of lips. Dyspnea. Over the left lower lobe posteriorly there is marked dullness, percussion tenderness, loud bronchial breathing and voice, some sticky râles. No abnormal signs over the right lung. *Diagnosis*: Abscess of the lung, empyema.

From the foregoing it is noteworthy that the customary diagnosis of pneumonia with empyema was not made in this case. It should also be noted that the existence of fetid sputum was sought because a putrid abscess was suspected. This truly progressive outlook on the subject of acute putrid pulmonary abscess must be regarded, I believe, as quite in advance of views which are rather generally held at the present time.

Clinical events and course. On admission the patient was uncomfortable, complaining chiefly of a frequent but essentially unproductive cough. An x-ray taken shortly after admission revealed (especially in the lateral view) two homogeneous areas of density apparently representing paramediastinal and intrapulmonary collections of fluid. The dramatic evolution of an alarming picture indicative of spread of infection within the lung and pleura, with self-revelation of its underlying putrid character is best seen in the following notes taken from the nursing chart. The value of notes made by well trained nurses is also illustrated:

- November 7, 2:00 p.m. Coughing at frequent intervals.
2:45 p.m. Coughing severe, non-productive. Codeine given.
5:15 p.m. Coughing severe, not relieved by codeine. Morphine given.
10:15 p.m. Coughing almost constantly. Dyspnea. Slight amount of foul sputum at times. Morphine administered.
November 8, 12:15 a.m. Morphine and codeine for cough and restlessness.
6:45 a.m. Cyanosis now present. Foul sputum at times.
8:30 a.m. Severe coughing spell lasting a half hour. Sputum foul-smelling.
8:45 a.m. Color poor. Profuse diaphoresis. Respirations 34, labored. Pulse 120.

The patient's condition on the morning of November 8 was truly precarious. It was reminiscent of the alarming picture, seen a number of years ago in a case of unrecognized undrained putrid empyema which went on to a fatal termination in fifteen days from the onset of symptoms. A report has been made elsewhere¹ concerning the course of events in these cases. To quote briefly: "The course may at times be hyperacute and fulminating. In our series there are a few instances in which patients were in a profoundly septic state within a week of the onset of symptoms. On the other hand, well-defined encapsulation of a small putrid empyema may lead to a relatively mild and benign clinical course."

Operation. In the case under consideration, an operative indication appeared clear despite the patient's condition. Collections of foul pus in the pleural space being present (presumably), their drainage was imperative regardless of the pulmonary lesion which was assumed to exist and to be extensive. Operation was performed under local anesthesia on the morning of the day after admission. It consisted essentially of the removal of liberal segments of two ribs through a posterolateral approach and the entry and unroofing of two large putrid empyemata. Of the latter, one was situated in the paravertebral zone and the other was chiefly intrapulmonary. A third smaller collection was parapericardial. All intercommunicated by narrow tracts. The shelf of pulmonary tissue between the two main pockets was densely infiltrated, and was the apparent source of the pleural infection. In this case a bronchopleural fistula did not appear after operation and the precise site of the causative pulmonary focus could not be ascertained.

Postoperative course. There was immediate improvement following the wide drainage which was instituted at operation. Cough, dyspnea, and cyanosis subsided promptly after operation, and the patient's general condition improved rapidly. The progress of the wounds was satisfactory, but fever continued for two weeks after operation apparently due to continuation of the infection within the lung.

The wounds healed. The patient was discharged symptom-free and has remained so.

¹Neuhof, H. and Hirshfeld, S.: Putrid Empyema. Ruptured Putrid Abscess of the Lung. *Ann. Surg.* 100: 1105, 1934.

COMMENT

This case illustrates the thesis that there should be more general recognition of that variety of putrid empyema which masquerades as "pneumonia with pleural effusion." Its usual outstanding features, in contrast to those of pneumonia, are initial severe thoracic pain, essentially unproductive cough, and the physical signs (by percussion) of early pleural effusion. These features should lead to the prompt consideration of the existence of putrid empyema, particularly in the presence of poor dental hygiene. Promptness is emphasized because the prompt institution of adequate surgical drainage implies the likelihood of freedom from mortality.

A NEW METHOD FOR THE TREATMENT OF LEUCOPENIC STATES

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The present treatment of leucopenic states is unsatisfactory. Nucleotide therapy has not been generally accepted. Transfusion, with the prime object of conveying leucocytes rather than plasma or red blood cells, is the main reliance as palliative therapy, but is of limited effectiveness. These patients are usually not anemic.

The number of leucocytes in the standard transfusion is too small to meet the need of the leucopenic patient. Any method by which the number of leucocytes transfused could be increased several fold might have value. Such a possibility exists. In normal persons the injection of a variety of substances, such as foreign proteins, vaccines, adenine and other nucleic acid derivatives, produces a temporary leucocytosis of fifteen to thirty thousand cells or an increase of three to six times the normal. These substances, when injected into the patient, generally fail to produce an increase in leucocytes because of the damaged bone marrow.

The method proposed is to induce leucocytosis in a donor and to transfuse when his white blood count is at a sufficiently high level.

The author chose the intravenous injection of typhoid vaccine because he was familiar with the very prompt leucocytosis so produced (1).

CASE REPORT

History. J. B., a 20 month old girl,¹ was first seen on October 19, 1939. She had been well until two weeks previously, when she developed fever, an acute sore throat, and a generalized eruption suggesting scarlet fever. She received sulfanilamide, 5 grains every four hours, a total of 15 grains. The only other medication was sodium salicylate, 10 grains. She apparently improved for over a week.

She then developed fever, ranging from 103° to 105° F.; a suppurative otitis media, an acute pharyngitis and an extensive impetiginous rash of the face; she appeared desperately ill. A blood count at this time showed an almost complete disappearance of granular leucocytes; hemoglobin, 71 per cent (Salhi); red blood cells, 4,560,000; white blood cells, 9,100 with .5 per cent polymorphonuclear leucocytes; 89.5 per cent small lymphocytes; 10 per cent large mononuclear cells.

A transfusion of 300 cc. of citrated blood was given from the father. There was slight clinical improvement, the temperature dropped to 101.5° F. for a few hours. Immediately after the transfusion the blood count showed: white blood cells

¹ The author is indebted to Dr. A. Wainston and to Dr. Joseph C. Ehrlich, pathologists to the Royal Hospital, Bronx, New York for supplying him with various details.

12,000, 15 per cent granulocytes (4 per cent juvenile forms, 4 per cent staff forms and 7 per cent polymorphonuclear leucocytes), 66 per cent small lymphocytes, 19 per cent large mononuclear cells. The toxic symptoms and fever, however, persisted.

It was decided to give the patient another transfusion from the same donor after inducing leucocytosis in him. On the evening of October 19 the father was, therefore, given an intravenous injection of 15 million killed typhoid bacilli. A few hours later he had a severe chill and his temperature rose to 104°F. On the morning of October 20 his leucocyte count had risen from 10,500 to 28,500. A transfusion, this time of only 150 cc. was then given to the child. The immediate clinical result was startling. The temperature, which before the transfusion had again risen to 105°F., dropped within a few hours to 101.5°F. and then to normal. The child's blood count the day after the transfusion showed 10,800 leucocytes, 34.5 per cent granulocytes (2 per cent juvenile, 6.5 per cent staff, 23 per cent polymorphonuclear neutrophils, 2.5 per cent eosinophiles, .5 per cent basophiles) 53 per cent lymphocytes, 12.5 per cent large mononuclears. The child subsequently recovered completely.

COMMENT

It is not claimed on the basis of this one case that the cure was unquestionably due to the treatment. However, before transfusion the patient had almost complete agranulocytosis; her condition was becoming steadily worse and she gave the impression of total lack of resistance to infection so typical of agranulocytosis. The first transfusion of normal blood produced a slight increase of leucocytes, but no change in symptoms in contrast to the startling change in both the symptoms and granulocytes following the second transfusion of specially stimulated blood from the identical donor.

The result may have been due not so much to the actual number of leucocytes transfused (which was not large) as to the passive transmission of a bone-marrow stimulating factor. It is known (2) that in agranulocytosis the bone marrow is not actually destroyed but is often normal or even hyperplastic. The possibility exists, therefore, that it lacks only some maturation factor which can be supplied by the blood of a suitably stimulated normal individual.

The preliminary preparation of donors by vaccine injections has been tried before, but not for the purpose, increase of donor's leucocytes, here presented. The "immuno-transfusion" of Sir Almoth E. Wright (3) was given two to six hours after the donor had received a subcutaneous injection of staphylococcus vaccine. Its object was to take advantage of a transient, though slight, increase in non-specific bactericidal power of the donor's blood. After a rather inadequate clinical trial (4) it seems to have been dropped.

The present report is offered in order that others may try this method of transfusing leucocytes in leucopenic states. There are several questions which will have to be answered: 1) Is blood containing a great number of leucocytes more effective than the standard transfusion? Assuming that it is, 2) what is the best leucocyte stimulant to inject in the donor?

- 3) How long do the transfused leucocytes remain in the circulation? 4) Is there any stimulating effect on the myeloid cells of recipient's bone marrow?

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ELECTROCARDIOGRAMS WITH NORMAL LIMB LEADS AND WITH ABNORMALITY IN ONLY ONE OF FOUR PRECORDIAL LEADS

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A group of 187 electrocardiographic records was selected from a large series, each record showing an abnormality of the curve either in the limb leads or in one or more of the four precordial leads recorded. Records showing bundle branch block were excluded as well as records showing the influence of digitalis. The precordial leads were those recommended by the author (1) and are called EF2 (upper end of ensiform and left parasternal line), EF3 (half way between EF2 and 4F), 4F (just lateral to the cardiac apex), and CF5 (at the level of 4F in the anterior axillary line). The last two are leads recommended by the American Heart Association, the first two are obtained from points just below those from which Leads CF2 and CF3 of the Heart Association are obtained. The usual standards for normal limb leads were adhered to and for the precordial leads it was decided, after reviewing the normal series of Barnes (2) and of Shipley and Hallaran (3) to consider that the T wave was abnormal if inverted or diphasic in any of these leads or if its amplitude was less than 1.7 mm. in Lead EF2, 1.2 mm. in Lead EF3, 1.3 mm. in Lead 4F and 1.2 mm. in Lead CF5.

In this group of 187 records 14 were found with normal limb leads and an abnormality in only one of the four precordial leads. In 4 of these the abnormality was of QRS alone there being an absent or small R in Lead EF2. In the other 10 the T wave alone was abnormal. None had an abnormal QRS combined with an abnormal T in the same lead. Of the 10 with T wave abnormality in one precordial lead the abnormality was in Lead EF2 in 5 records and in Lead CF5 in the other 5. Figure 1 shows the records of the precordial leads of 5 of the cases, two with abnormality of T in Lead EF2 and two with abnormality of T in Lead CF5. The last record shows an abnormality of QRS in Lead EF2 there being no R wave in this lead but only a QS deflection.

The cases are arranged in table 1 to show the electrical axis of QRS and the direction of the T waves in the limb leads as well as the character of the T waves of the precordial leads. It will be observed that all records with abnormal T in Lead CF5 had an upward T in all three limb leads and all but one had T_1 of less amplitude than T_3 . It is also seen that all but

one of those with abnormal T in Lead EF2 had the T wave directed upward in Leads I and II and downward in Lead III. The exception, Case 6, had a small upwardly directed T_3 while T_1 and T_2 were larger

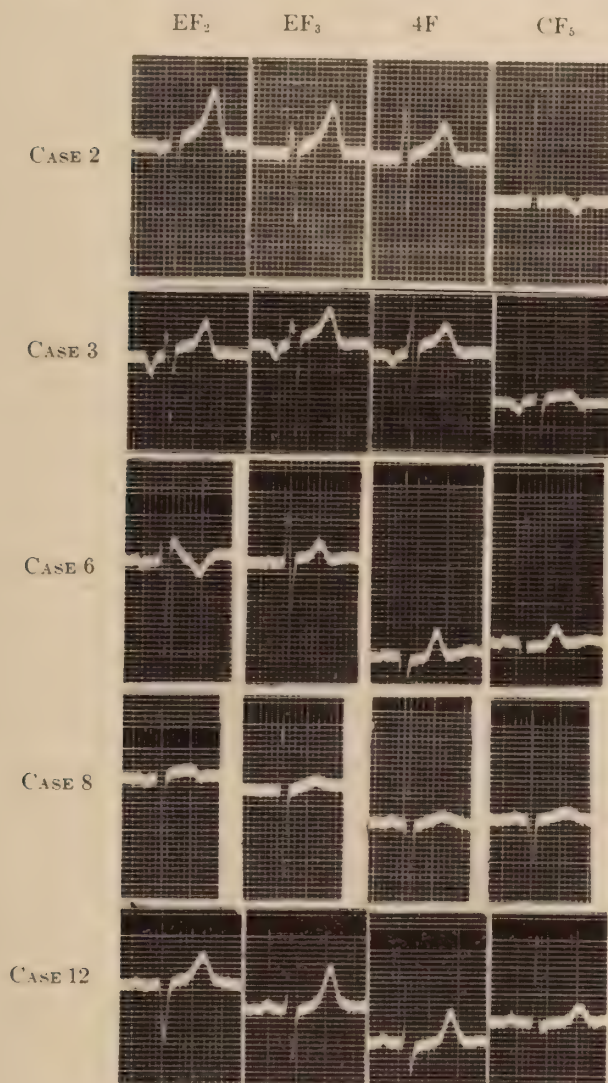


FIG. 1

and upward. This table suggests the possibility that a small or inverted T_1 might be uniformly associated with inversion of the T wave in Lead CF5 and that an inverted T_3 would be associated with inversion of T in Lead EF2. Further study of other cases of the series proved that this

was not at all the case. It was found, however, that a small or absent R in Lead EF2 was often associated with marked left ventricular hypertrophy as has been pointed out by others (4).

The chief interest in these cases lies in the fact that they reemphasize the importance of obtaining more than one precordial lead in all cases (5) and illustrate the character of the abnormality which is found in such records. To use more than one precordial lead is especially important in cases with normal limb leads for in these the precordial leads give the only abnormal indication of the record. It is important also to note that

TABLE 1

CASE	QRS	T	EF2	CF5
1	L. axis slight	+++ , $T_1 < T_3$	Normal	-
2	L. axis +	+++ , $T_1 < T_3$	Normal	-
3	L. axis slight	+++ , $T_1 < T_3$	Normal	+ -
4	L. axis definite	+++ , $T_1 < T_3$	Normal	±
5	L. axis +	+++ , $T_1 > T_3$	Normal	±
6	L. axis slight	+++ , $T_1 > T_3$	-	Normal
7	L. axis +	++-	+ -	Normal
8	L. axis slight	++-	+ -	Normal
9	L. axis +	++-	±	Normal
10	Normal axis	++-	±	Normal
11	L. axis +	++-	Small R	Normal
12	L. axis +	++(+ -)	Absent R	Normal
13	L. axis +	+++	Absent R	Normal
14	L. axis definite	++-	Absent R	Normal

+ -, T wave diphasic the + phase preceding the -.

±, T wave amplitude less than standard.

-, T wave inverted.

the abnormal feature is sometimes in Lead EF2 and sometimes in Lead CF5 and because of this it is advisable to obtain both of these leads.

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SOME COMPENSATORY MECHANISMS IN HEART FAILURE

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The clinician and physiologist have divided cases of heart failure into two large categories. Based upon current conceptions of the mechanisms concerned in their pathogenesis, these have been called "forward failure" and "backward heart failure". We will use the term "forward failure" in the sense in which it is used by Harrison (1) as including disturbances usually spoken of as "collapse", "primary shock", "secondary shock", etc. This is contrasted with "backward heart failure" which manifests itself clinically by abnormal fullness of the veins. While the former is usually of peripheral origin the latter is always of cardiac origin and is the state usually called "congestive heart failure".

In some work previously reported we have studied the characteristic anatomical changes in the gastrointestinal tract, found in "forward failure" (2). This was done in an effort to investigate the mechanisms involved in the production of these lesions. We concluded that these lesions were the result of the vasoconstriction occurring in "forward failure" and forming one of the homeostatic mechanisms invoked by the organism to maintain the circulation to the heart, lung and brain. These lesions were reproduced in model experiments using adrenalin to simulate the vasoconstriction which clinically resulted from widespread activity of the sympathetic portion of the autonomic nervous system (3).

In order to obtain control observations for purposes of comparison we examined the gastrointestinal tract in cases of "backward heart failure". We were then struck by the relative paucity of anatomical findings, both gross and microscopic, in cases with clinically profound congestive heart failure. Grossly, even in cases of severe myocardial insufficiency nothing more than congestion of varying degree was observed, even in the presence of an enormously enlarged liver. Microscopically the findings were even less marked and consisted in a moderate dilatation of the submucosal veins, usually but not always associated with capillary congestion in the villi. Microscopic foci of edema were seen in the villi of the small intestine in only three of our seventy cases, and was minimal in degree. In none of our cases were erosions or ulcerations present, such as we have observed in "forward failure". We have noted that the capillary congestion in the small intestine is either exclusively or predominantly mucosal, rather than submucosal as witnessed in cases of "forward failure". There was

also no close correlation between the severity of the heart failure and the degree of intestinal change.

The presence of only such minimal changes in the gastrointestinal tract in congestive failure is difficult to understand. Based upon current physiological concepts of back pressure stasis we would expect to find a very profound congestion of the intestinal tract which in fact, was either absent or not very striking.

From the work of Burton-Opitz (4) and others (5) it is well known that the venous pressure at the point of origin of veins, *i.e.*, at the venous end of the capillaries, is greater than at any point nearer the right auricle. As he has demonstrated, normally the highest venous pressures in the circulatory system are found in the mesenteric veins. He, as well as Krogh (6), has pointed out that this is due to the fact that the entire portal vein system is intercalated between two capillary beds which may be regulated independently of one another. According to the back pressure concept it would thus be expected that the increased pressure transmitted from the right auricle through the inferior vena cava and hepatic veins to the liver would, by hindering the exit of blood from the portal vein and obstructing the flow of blood to the heart, cause stasis in the intestinal tract. Similarly this would imply that in long standing heart failure and its occasionally accompanying cardiac cirrhosis, there would be an increase in caliber of the portal vein and its tributaries accompanied by congestion of the intestines and splenic enlargement. Likewise, it would be expected that in such cases, a phlebosclerosis of the portal vein might develop. Actually, none of these phenomena are observed as part of the usual morphological findings in congestive heart failure.

As a result of the insignificant intestinal changes which we observed, we felt that it would be desirable to study the hepatic changes in this group of cases of "backward heart failure". This was done because of the lack of evidence of any significant vascular changes in the more proximal of the two capillary beds which control the flow through the portal vein, *i.e.*, in the vascular bed of the gastrointestinal tract. Furthermore, the pathologist has found the liver, lungs and heart to be the most profoundly involved organs in the usual case of heart failure, and has given especial attention to the study of the liver.

In this he has been greatly influenced by the physiological concepts of his clinical colleagues. As a result, the typical morphological changes in the liver described in cases of heart failure have been those which afforded anatomical support to the concept of "backward heart failure". To be sure, these changes were noted in cases of either severe or advanced heart failure. As a rule the changes consisted in a pronounced dilatation of the central lobular vein which was filled with blood. This dilatation is also described as extending from the central vein into the sinusoids for a varying distance toward the periphery of the lobule. In such cases, a pressure

atrophy of the central portion of the liver cords may be noted or there may be centrolobular hemorrhage and necrosis leading to disappearance of these cells.

While recognizing the validity of this description, objections to the underlying concept of back pressure as a pathogenetic mechanism began early (7, 8, 9, 10). Thus, it was pointed out that if back pressure were the cause of the congestion and necrosis, one would expect a very uniform distribution of such changes in the liver. While gross differences in the extent of the anatomical alterations may be explained on the basis of differences in caliber and angle of entrance of the hepatic veins (10), this certainly would not explain striking differences in the degree of anatomical change from lobule to lobule within any given small microscopic area of liver. Marked variations in the intensity of congestion between adjacent lobules has been known to exist for many years (8, 9, 10) and from our observations is an almost regularly occurring phenomenon. The same is true of the cellular changes in the liver cords. We have observed, in studying individual lobules in cases of "backward heart failure", that the congestion while uniform and centrolobular in distribution in severe and in advanced cases, did not have that distribution, uniformly, in the early and mild cases. In such instances we have observed distinct variations in the degree of sinusoidal congestion in a given group of sinusoids. Occasionally we have seen a midzonal congestion such as that described by Lambert and Allison (11). We do not feel, however, that this forms a special type of hepatic congestion. We have seen this midzonal congestion in livers in which other lobules showed other varieties of distribution of the congestion.

Despite the increase in pressure in the right auricle and inferior vena cava the direction of blood flow in the veins is still toward the heart. This indicates that the pressure in the portal vein is still higher than that in the hepatic veins and that the pressure gradient is still downward from the portal vein to the hepatic veins. The rate of fall may be, and probably is, less due to the elevation in both portal vein and inferior vena caval pressures. Thus, the rate of blood flow is decreased and the pressure in the sinusoids raised. The latter must also show a pressure gradient with a maximum pressure at the periphery of the lobule and not at its center.

As a result we might further expect the mechanical effects of backward pressure in the portal circuit to be manifested by increased portal vein pressure, dilatation and phlebosclerosis of the portal vein, splenomegaly, dilatation of the mesenteric veins, and edema and congestion in the gastrointestinal tract. This is the picture found in hepatic vein thrombosis as reported in the literature (12, 13) and as observed in two similar cases which we studied for comparison. We might also expect the formation of a collateral circulation in longstanding cases of heart failure. Further-

more, Harrison (1) emphasizes increased venous pressure as a cause of edema in "backward heart failure". The marked permeability of intestinal capillaries is recognized (Starling (14)) and we would, therefore, expect to find gross intestinal edema in "backward heart failure" as we often do in cases of hepatic or portal vein thrombosis. For the same reason we would expect to find the almost invariable occurrence of hepatic edema in such cases since the sinusoids are among the most permeable vessels in the body. As Drinker and Field (15) point out, the permeability of the liver sinusoid is apparently complete for all save the formed elements of the blood, and if the pressure in the sinusoid is increased, even the formed elements may pass through. This extreme degree of permeability balances a low pressure in the lobular vessels. However, actually, Keschner and Klemperer (16) observed such edema in only 39 per cent of their cases of cardiac failure.

We are, therefore, unable to ascribe the anatomical changes in the liver and the relative lack of anatomical findings in the gastrointestinal tract solely to backward pressure, especially since some of the livers showing typical congestion were observed in patients who during life manifested no elevation of peripheral venous pressure.

It has been customary to consider the basic disturbances in "forward failure" to consist in a discrepancy between the capacity of the vascular bed and the amount of blood available for circulation. The causes of such a discrepancy are extremely numerous and variable in nature. We have discussed elsewhere (3) the mechanisms whereby such a state of affairs may lead to anatomical changes in the viscera, as a result of the compensatory mechanisms which function to maintain an adequate circulation to vital organs. In such a state of affairs the heart receives an amount of blood from the venae cavae which, although completely discharged from the left ventricle, may be insufficient to nourish the tissues. The organism responds with a characteristic compensatory vasoconstriction which permits a redistribution of blood in accordance with tissue needs.

The problem in "backward heart failure" is in many respects the reverse of that found in shock. Here, we are dealing with a heart which for one reason or another is unable to empty itself of the amount of blood returned to it from the venae cavae. As a result of this, varying amounts of blood remain in the right auricle and adjacent venae cavae at the end of auricular systole. In this way there results a tendency to an increase or an actual increase in pressure within these structures. It was shown in 1914 by Bainbridge (17) that these areas of the cardiovascular system are capable of acting as points of origin of afferent stimuli to the medulla. Anatomical confirmation of the presence in these areas of afferent sensory nerve endings was given by the work of Nonidez (18) who showed such endings in the subendothelial tissue of the superior and inferior venae cavae and in the

posterior auricular wall between them. In 1924 MacDowall (19) showed that there existed in the right auricular wall the sensory nerve endings of a cardiovascular reflex arc, which is not only accelerator, as shown by Bainbridge, but also pressor, analogous to the inhibitor-depressor reflex of the left side of the heart. He found that when the venous pressure was low, impulses passed up by way of the vagus to the vasomotor center and reflexly increased vasomotor tone and thus served to maintain the circulation. In this fashion an increase in venous pressure would serve to cause a decrease in vasomotor tone, a relaxation of arterioles, capillaries, venules and veins so as to increase the capacity of the circulatory bed, and thus counteract any tendency to an increase in venous pressure. That these reactions are of reflex origin is shown by the fact that they are abolished by vagotomy. By direct oncometric studies on the inferior vena cava, Schretzenmayr (20) showed that an increase in right auricular pressure reflexly acted to increase the capacity of this vein. As he points out, this reflex dilatation of the cavae when the heart cannot manage the blood returned to it, is the reverse of the Bainbridge reflex in that the stimulus originates in the heart and acts on the vein, whereas in the Bainbridge reflex the stimulus arises in the venae cavae or adjacent right auricle and acts on the heart to cause an increase in rate.

Johansson and Tigerstedt (21) in 1889 studied the effect of infusion of saline or blood into animals and found that this did not cause any significant changes in blood pressure or pulse rate. They observed that the total volume infused into a vein did not remain in the actively flowing circulation for any length of time, but was taken up by the liver and withdrawn from the general circulation. Five years later Bayliss and Starling (22) investigated this same problem and found that such an intravenous injection caused a rise in the pressure in the portal vein which occurred before and was somewhat greater in degree than the corresponding changes in the inferior vena cava. They found that the excess fluid was distributed to the venous side of the circulation. Since both portal pressure and vena caval pressure rose, there was obviously an increase in the pressure within the hepatic capillaries at least at the periphery of the lobule. Since the hepatic sinusoids dilated to receive the excess blood volume and the blood flow from the hepatic veins decreased there must have been a diminution in the gradient of pressure from the periphery to the center of the lobules. In this fashion the blood is stored in the dilated sinusoids at a pressure sufficiently low to prevent a rapid outflow. As a result Bayliss and Starling pointed out that the hyperemia which they observed in the liver was not passive but active hyperemia. They pointed out that the direct measurement of pressure in the portal vein and vena cava simply bore out the fact which had been so often observed anatomically, namely, a swelling of the liver, which is extremely full of blood. Jarisch and Ludwig (23) in 1927, using very small amounts of fluid, made essentially the same ob-

servations and indicated the importance of the liver and intestinal tract in adjusting the capacity of the circulatory system, when artificial increase or decrease in blood volume was caused. In these experimental studies the increase in volume of circulating blood caused a rise in pressure in the large veins and right auricle and thus reproduced a basic phenomenon present in "backward heart failure". The resultant compensatory phenomena whose function would serve to maintain circulatory equilibrium and efficiency, reflexly lead to the congestive phenomena observed in such states where the circulatory blood volume is either temporarily or permanently greater than the heart can distribute. This is fundamentally the state of affairs which is present in clinical "backward heart failure".

These pressor-depressor reflexes through the vasomotor center also cause volume changes in the vascular bed of other organs. Thus, Tournade (24) has shown that depressor stimulation causes vasodilatation in the kidneys and Francois-Franck and Hallion (25) have noted similar reactions in the pancreas, while Barcroft and Nisimaru (26) as well as Masuda (27) and Heymans *et al* (28) have observed a similar phenomenon in the spleen.

The anatomical counterpart of such a reaction to an increase, or to a tendency to an increase in pressure within the cavae and right auricle is seen in the clinically observed hepatomegaly, occurring in heart failure, in the presence of a normal venous pressure. This we interpret as evidence that the pressor-depressor reflexes are active and that the increase in vascular bed of the liver has been able to withdraw from the active circulation an amount of blood sufficient to prevent a rise of pressure in the larger veins and right auricle. If this compensation is only temporarily effective, the venous pressure will eventually rise above normal. Obviously compressing such a liver and mechanically increasing the flow to the right heart may cause the venous pressure to rise. This is a frequent clinical observation.

Anatomically such a liver shows a very mild congestion which varies markedly from lobule to lobule. There may also be distinct variations in the degree to which the individual sinusoids in a given lobule may be congested. With severe myocardial insufficiency, *i.e.*, when the heart has such slight reserve that the reservoirs are reflexly utilized to their fullest capacity, one sees more marked hepatic changes. It is in the livers from such cases that the textbook picture of almost uniform centrolobular congestion, hemorrhage and even necrosis or atrophy is derived. However, even in such cases it is not infrequently possible to find distinct and striking differences in degree and distribution of the anatomical changes.

In these advanced cases of cardiac failure in which we have clinical evidence that the compensatory liver mechanism has failed to prevent a rise in venous pressure the elevation of the latter must contribute to the engorgement of the liver. This, however, must occur only after the reservoir function of the liver has been utilized to its fullest capacity. For this reason it is difficult in such advanced cases to evaluate the relative im-

portance of backward pressure and compensatory active congestion in the causation of the hepatic changes seen at necropsy.

Naturally, similar mechanisms function in the other abdominal viscera. We have, however, limited our study to the liver and gastrointestinal tract.

One of the usual physiological consequences of congestive heart failure is a reduction in cardiac output. The stroke volume decreases so that the minute volume output drops despite the tachycardia which is usually present. Actually the arterial blood pressure either remains unaltered or may even rise.

The aorta and carotid sinuses contain within their walls sensory nerve endings which respond to changes in pressure within these vessels. Should



FIG. 1. Liver showing an eccentric distribution of the centrilobular congestion in congestive heart failure (photomicrograph, $\times 105$).

the pressure within them tend to decrease there occurs a reflex vasoconstriction which mainly affects the visceral vascular bed. Obviously under these circumstances one may have a diminution in oxygen supply to the tissues despite a normal oxygen content of the arterial blood. In the usual case of congestive heart failure as seen at necropsy anatomical evidences of such anoxemia, resulting from vasoconstriction as we have described elsewhere (2), are not pronounced.

However, cases do occur in which one sees anatomical evidence which can be interpreted as combinations of both "backward heart failure" and "forward failure". Such cases are sometimes seen when during the course of a period of "backward heart failure" a complicating pulmonary embolization or coronary occlusion occurs. With this, one observes clin-

ically the sudden superimposition of a shock-like state in a picture which had previously been characterized by congestive heart failure. Under such circumstances one may find focal lobular necrosis in the liver, while during life jaundice may have been noted.

The observations which we have recorded, when considered in the light of the reflex vasomotor phenomena which we have mentioned compel us to interpret the changes in the liver and intestine, as due to an active congestion initiated and regulated by vaso-depressor reflexes, whose afferent arc has its origin in the venae cavae and right auricle rather than primarily to a backward pressure due to overfilling of the veins by the heart. Thus, these lesions represent more the anatomical result of the compensatory vasomotor changes which are brought into play to prevent overloading of the heart, than the exclusive effect of back pressure.

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THE INFLUENCE OF PROTEIN METABOLISM ON THE DISTRIBUTION OF NITROGEN COMPOUNDS IN THE LIVER

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In recent years numerous papers on fat and carbohydrate metabolism, as well as on liver ferments, hormones, and vitamins, have greatly clarified the important rôle of the liver in metabolism. Our information about the relations of the liver to the total protein economy, nevertheless, still remains very limited. The influence of the liver on the protein content of the blood has been as clearly recognized by experimental pathologists as by clinicians. Of significance is not only the fact that the liver produces fibrinogen; even more important is the observation that the albumin-globulin ratio in liver disease shifts in the direction of a globulin increase. The importance of the liver for protein metabolism can be demonstrated as well by the widespread clinical use of protein precipitation reaction in the blood of patients with liver disorders, as, for example, the Takata and Weltmann (1) reactions which are probably caused by the appearance of altered proteins. Finally, we know from the liver-extirpation experiments of Mann and Magath (2) that the complete failure of urea production is accompanied by an increased amino acid content of the blood in hepatectomized animals; the excretion of tyrosine and leucine in acute liver atrophy has been known ever since its discovery by Frerichs.

As limited as our knowledge of the liver's influence on protein and nitrogen metabolism in the blood may be, even less is known about the changes of the protein and other nitrogen compounds in the normal and diseased liver. Earlier investigations (3) have confirmed the belief that the protein content of the liver in acute and chronic liver atrophy is significantly decreased, but the non-coagulable nitrogen is relatively increased; on the other hand, in cloudy or albuminous swelling, liver protein doubles (4). More recent investigations on the behavior of liver-nitrogen under pathological conditions have been performed by Elias and Kaunitz (5) and their collaborators. They have shown that in the rabbit's liver oxygen deficiency produces a loss of protein, but at the same time an increase of the non-protein nitrogen, especially the nitrogen of urea and amino acids. Similar changes also occur in the livers of dogs in which pancreas-diabetes has been induced experimentally. It is noteworthy that in both instances

normal conditions may again be restored through the administration of dextrose or insulin.

At this stage of our knowledge it seemed to be of interest to investigate the behavior of liver-nitrogen under the influence of various dietary disturbances and poisons which produce changes in protein metabolism. For this purpose the following experiments were performed.

MATERIAL AND METHODS

The experiments were carried out on guinea pigs which were prepared in the following ways: 1) in some *scurvy* was induced by a vitamin C-free diet; 2) others were given *thyroxine* for various lengths of time; 3) some were treated with *theophylline*; 4) still others with *calomel*; and finally 5) separate experiments were made on guinea pigs sensitized with *horse serum*.

In previous experiments one of us (6) found it convenient to determine the percentage-ratio of non-coagulable nitrogen to total nitrogen:
$$\frac{\text{non-coagulable nitrogen}}{\text{total nitrogen}} \times 100$$
 (which will be referred to herein as the nitrogen coefficient). Male guinea pigs of 250 to 300 gm. weight were used. For three to four weeks they were kept on a diet consisting of a mixture of 80 per cent ground oats and 20 per cent bran; in addition, 5 cc. of lemon juice were administered daily to each animal (Diet I). In some experiments the diet consisted of oats and fresh cabbage leaves as a source of vitamin C (Diet II). In the *scurvy* experiments the guinea pigs were fed oats and bran without lemon juice or cabbage. In the *thyroxine* experiments diet I was used; 0.1 to 0.2 mg. of *thyroxine* were injected for four to six consecutive days. Twenty-four hours after the last injection, the animals were killed by bleeding. The *theophylline* animals received diet I for eight days, and were then injected subcutaneously on every third day of a fourteen day period with 0.12 mg. of *theophylline* sodium acetate per 1 gm. body weight; on the fourteenth day after the beginning of the treatment they were bled. The animals treated with *calomel* were kept on diet II; 0.1 gm. of *calomel* was suspended in water and administered orally by syringe; twenty-four hours later the animals were killed by bleeding. Sensitizing by *horse serum* was accomplished by subcutaneous injection of 0.5 cc. of serum; fourteen days later the animals were killed. The determination of total nitrogen and non-coagulable nitrogen in the liver pulp was performed as described in the paper of Hashimoto and Pick (6).

RESULTS

1. *Nitrogen coefficient in the liver of normal guinea pigs.* Fourteen animals were used for the determination of normal values, and were fed a vitamin-rich diet for three to four weeks. Nine of them received diet I and five of them received diet II. The mean values of the liver-nitrogen

in the first group were as follows: Total nitrogen (T.N.), 3.25 per cent; non-coagulable nitrogen (N.P.N.), 0.35 per cent; the nitrogen coefficient being $\frac{\text{N.P.N.}}{\text{T.N.}} \times 100 = 10.7$, with a standard error of ± 0.2 . The mean values of the second group were as follows: Total nitrogen, 3.47 per cent; non-coagulable nitrogen, 0.35 per cent; and the nitrogen coefficient = 10.0, with a standard error of ± 0.3 . The percentage-ratio of the non-coagulable nitrogen to the total nitrogen in the liver of the normal guinea pig thus fluctuates between 10.0 and 10.7.

2. *Nitrogen coefficient in the liver of scurvy guinea pigs.* The results of the analysis of scorbutic livers show a significant deviation from the normal guinea pig livers. The mean values of scurvy livers are: Total nitrogen, 3.33 per cent; non-coagulable nitrogen, 0.47 per cent; the nitrogen coefficient being 14.1. The fact that the livers of scorbutic animals contain a larger amount of non-coagulable nitrogen substances than the normal liver may well be related to the evident inability of vitamin C-deficient animals to carry out many syntheses necessary for cell growth (7). It is well known, for example, that collagen formation ceases (8) in animals and humans with ascorbic acid deficiency; that wounds heal badly or not at all (9); that the first and sometimes the only morbid effect of C-avitaminosis is capillary fragility (10); that the antibody production is greatly diminished (11); and that only the addition of ascorbic acid restores the lost ability to the normal level. Levine and his collaborators (12) recently observed that premature infants receiving diets of relatively high protein content and vitamin C-free cow's milk exhibit a spontaneous defect in their metabolism of tyrosine and that of phenylalanine; this defect is manifested by the excretion of *p*-hydroxyphenyl-lactic and *p*-hydroxyphenyl-pyruvic acids in the urine. Vitamin C administration abolishes the urinary excretion of these abnormal metabolites. Sealock (13) and his associates found that the feeding of *l*-phenylalanine to vitamin C-deficient guinea pigs results in the excretion of tyrosine metabolites such as *p*-hydroxyphenyl-pyruvic acid, homogentisic acid and an α -keto-acid. Administration of ascorbic acid promptly prevents the excretion of these metabolites. The question, however, whether at this point there also exists a specific incompetence of the liver to utilize supplied nitrogen products cannot be decided without due consideration of the general disturbance of metabolism. All the scorbutic guinea pigs suffer proportionally large losses of weight. In our animals this loss varied between 16.1 and 43.5 per cent of the original weight. It is probable that this rapid catabolism in the tissues causes the change in the nitrogen coefficient in the liver, although vitamin C deficiency itself undoubtedly constitutes the initial cause of this phenomenon.

Our assumption that the changes in the liver's nitrogen coefficient are non-specific is supported by further experiments with substances which,

though acting in a different way, induce a rise in metabolism and a disintegration of proteins. For this purpose, thyroxine, calomel, and theophylline were administered.

3. *Nitrogen coefficient in the liver of guinea pigs treated with thyroxine.* Although on a vitamin-rich diet, the nine animals of this series lost from 8 to 17.4 per cent of their initial weight, in spite of this, the total nitrogen in the liver amounted to 3.43, the non-protein-nitrogen to 0.37 per cent and, therefore, the nitrogen coefficient did not deviate significantly from the normal; it yielded a mean of 10.8 which about corresponds to the normal guinea pig liver. This demonstrates that a moderate loss of weight, caused mainly by increased degradation of fat and glycogen and accompanied by only a slight destructive metabolism of proteins, had no effect upon the nitrogen coefficient of the liver. This coefficient, however, was enhanced in two animals which were subjected to prolonged thyroxine treatment, and which showed severe cachectic symptoms. They suffered a loss of weight of 24.5 and 31.2 per cent respectively, with a nitrogen coefficient in the liver of 13.8 and 16.6. These values correspond to the nitrogen coefficient values observed in scurvy. Since it has been suggested (14), however, that the body's demand for vitamin C is increased in thyroxine poisoning, the question must be left open as to whether this increase of the nitrogen coefficient is a direct effect of thyroxine poisoning or is the result of vitamin C deficiency, which itself has been brought about by thyroxine.

4. *Nitrogen coefficient in the liver of guinea pigs poisoned by calomel.* In these experiments, in which the liver as well as the intestines were directly affected by calomel poisoning, profound and rapid changes in the protein metabolism of the liver could be observed. The six animals of this series showed a notable increase of non-coagulable nitrogen in fresh liver-pulp: the total-nitrogen yielded on the average 3.37 per cent; the non-protein-nitrogen, 0.50 per cent and the mean value of the nitrogen coefficient was 14.9. Here, too, the source of the protein-degradation-products stored in the liver is not known. Further experiments are planned to show how poisoning by metals and other organic substances affect the nitrogen coefficient of the liver and to explain more thoroughly the mechanism of these metabolic disturbances in the liver.

5. *Nitrogen coefficient in the liver of guinea pigs treated with theophylline and horse serum.* These substances, which have been investigated in numerous experiments, neither produced any considerable loss of weight nor disturbed the distribution of nitrogen in the liver. The mean value of the total nitrogen in the liver was in the theophylline animals, 3.13 per cent; in the sensitized animals, 3.35 per cent; and the non-protein-nitrogen was 0.33 and 0.35 per cent respectively. Thus, the nitrogen coefficient in these experiments was practically unchanged, and the mean values did not deviate significantly from the normal 10.4 and 10.5. Table 1 summarizes the results of the preceding experiments.

DISCUSSION

A survey of the accompanying table (table 1) reveals that the nitrogen coefficient (the percentage-ratio between non-coagulable nitrogen and total nitrogen) provides an interesting biological criterion for metabolism. It appears that this ratio remains constant and keeps within the narrow margin between 10.0 and 10.7. Only when the metabolism itself undergoes any really serious disturbance, such as in vitamin C-deficiency and in poisonings by calomel or prolonged thyroxine administration leading to severe cachexia, a shift appears in the nitrogen coefficient of the normal liver, and the liver is enriched in non-coagulable nitrogen. This increase in non-coagulable nitrogen, therefore, seems to be an ominous symptom of severe metabolic disturbance. Further investigations will have to determine the nature of the non-coagulable nitrogen products in the liver.

The opinions cited herein to the effect that only a severe metabolic disturbance changes the ratio of non-coagulable nitrogen to total nitrogen,

TABLE 1

NUMBER OF ANIMALS	TREATMENT	NITROGEN COEFFICIENT: $\frac{\text{N.P.N.}}{\text{T.N.}} \times 100$	STANDARD ERROR OF COEFFICIENT	LOSS OF WEIGHT IN PER CENT OF ORIGINAL WEIGHT
		N		
14	Normal animals	10.4	± 0.2	None
12	Scurvy	14.1	± 0.8	16.1-43.5
9	Mild thyroxine poisoning	10.8	± 0.3	8-17.4
2	Severe thyroxine poisoning	15.2	± 1.4	24.5-31.2
6	Calomel poisoning	14.9	± 0.4	
10	Theophylline poisoning	10.5	± 0.2	None
15	Sensitization with horse serum	10.4	± 0.2	None

and that well nourished animals show no change in the nitrogen coefficient even under the influence of substances such as moderate thyroxine or theophylline treatment, seem to indicate a different explanation for the results previously published by Hashimoto and Pick (6) on the intravital destructive protein metabolism in the liver of sensitized animals. These results were probably influenced by a deficiency in the diet of the sensitized guinea pigs. All our experiments on well nourished guinea pigs which were sensitized with horse serum yielded a normal nitrogen coefficient of 10.5 with a standard error of ± 0.2 . Protein sensitization alone does not seem to cause a change in the amount of non-coagulable nitrogen in the liver; and there is no basis for the assumption that protein sensitization leads to an "intravital autolysis in the liver."

SUMMARY

1. The nitrogen coefficient, the ratio in per cent of the non-coagulable nitrogen and total nitrogen ($= \frac{\text{N.P.N.}}{\text{T.N.}} \times 100$) in the fresh liver of normally

fed guinea pigs without disturbed protein metabolism remains constant and approximately amounts to 10.5.

2. In serious metabolic disturbances caused by *scurvy*, *calomel* poisoning, and severe *thyroxine* poisoning, the nitrogen coefficient is increased to 14.0 and above by accumulation of non-coagulable nitrogen compounds in the liver. In most cases, this change in the coefficient is correlated to the severity of the metabolic disturbance; it may thus provide a useful biological indicator of the actual extent of the metabolic upset.

3. Thyroxine, in doses which do not produce symptoms of severe thyrotoxicosis, or theophylline does not affect the normal nitrogen coefficient; nor does sensitization of guinea pigs with horse serum.

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THE RELATIONSHIP OF BENIGN AND MALIGNANT HYPERTENSION

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The clear differentiation between the benign and malignant forms of essential hypertension dates from Volhard & Fahr's classical monograph on Bright's Disease published in 1914 (18). Subsequent experience has done little more than amplify Volhard's clinical description of the two forms: the benign characterized by a moderate hypertension, good renal function, and ending after a long course in heart failure or cerebral hemorrhage; and the malignant, affecting an earlier age group, having a more severe hypertension and distinguished by the early development of albuminuric retinitis and subsequent rapid renal failure. To Fahr's description of the kidneys in the two forms, the "einfache blande sclerose" and the "kombinationsform," he himself added in 1919 (5) what has subsequently been recognized as the essential anatomical basis of the different morbid appearances, namely the occurrence in the "kombinationsform" of necrosing lesions and of endarteritis in the arterioles of the kidney and to a less extent in other organs except skin and muscle. One important question they did not answer—that of the relationship between the two forms—do they represent two manifestations of the same disease or are they from the start distinct entities. The essential features distinguishing the two forms are clinically the appearance of albuminuric or hypertensive neuro-retinitis and pathologically the occurrence of arteriolar necrosis in the malignant form. Recent work has thrown new light on the pathogenesis of these lesions and leads to a simple conception of the relationship between the two forms.

Although changes in the eyegrounds occur in both the benign and malignant forms of hypertension, the changes characterizing what used to be termed albuminuric retinitis, and is now called hypertensive neuro-retinitis or hypertensive neuro-retinopathy (7) are invariably met in the malignant form and are absent in the benign. The changes are bilateral and when fully developed comprise swelling of the nerve-head and retina, large ill-defined white patches around the disc, varying numbers of hemorrhages and a macular star figure; the retinal arteries are usually narrow and often show sclerotic changes, though they are frequently so obscured by edema in parts of their course that it is often difficult to be sure how much variations in calibre are truly the result of changes in their walls. Sometimes the first indication of the onset of neuro-retinitis is papilledema, but I have

seen cases in which a large ill-defined exudate in one fundus was the initial change. In benign hypertension some degree of retinal arteriosclerosis is the rule; otherwise the fundi are usually normal or, less often, show what Foster Moore first distinguished as arteriosclerotic retinitis and what Fishberg and Oppenheimer (7) prefer to call arteriosclerotic retinopathy. Here the changes are often unilateral; papilledema is uncommon and when it occurs is usually unilateral and often transient; the exudates are small and sharply defined and the macular star, if present, consists of dots rather than sheets or lines. That hypertensive neuro-retinitis results from the action of a toxin retained or liberated by a diseased kidney has now been abandoned in default of evidence, and it is now widely believed that the lesions are ischemic in origin. The evidence for this view is that the lesions are only found in association with hypertension which it is now known results from narrowing of the small arteries and arterioles, and that extreme narrowing of the retinal vessels is common in albuminuric retinitis. Opinions are somewhat divided as to whether the ischemia results from retinal arteriosclerosis or from vascular spasm. The chief proponent of the latter view is Volhard (16) who cites the generalized constriction of the retinal arteries seen ophthalmoscopically, and the absence of organic changes in the retinal arteries in two cases of albuminuric retinitis examined histologically by Schieck (14). Because he did not stain his preparations for fat, Schieck's findings have been criticized by Verwey (15) who found lipid changes in the retinal arteries of two cases of albuminuric retinitis. Friedenwald (8) also has demonstrated the frequency of lipid changes in the walls of retinal arterioles supplying the site of the focal changes in albuminuric retinitis and has stressed the frequency of organic changes in the central artery of the retina in cases where generalized narrowing of the visible retinal arteries is found. It is beyond my purpose to enter further into the controversy concerning the rôle played by organic and spastic arterial changes in the causation of the retinal lesions in hypertension, but I take this opportunity of recording that I have never seen localized retinal arterial spasm in hypertension, despite a persistent search for it over a number of years; in this my experience seems to coincide with that of most of my ophthalmological colleagues in this country.

A very different theory of the origin of albuminuric retinitis was put forward by Bordley and Cushing (3, 4) in 1908 who referred the lesions to raised intracranial pressure, for they found a raised cerebrospinal fluid pressure in many such cases and observed similar retinal changes in about 14 per cent of their brain tumors; further, they described a case of their own and quoted one of Bramwell's (2) in which the retinitis subsided after cerebral decompression.¹ In spite of the fact that a raised cerebrospinal fluid

¹ This seems to be an exceptional event. Grant (10) has described cases in which decompression was done for a suspected brain tumor in which both retinitis and raised cerebrospinal fluid pressure persisted after operation.

pressure has been described in many cases of albuminuric retinitis since Cushing and Bordley's time, their theory has never won support, because it fails to explain the striking difference between the typical retinal pictures of tumor of the brain and of hypertensive neuro-retinitis, and because a raised cerebrospinal fluid pressure is not invariable in hypertensive neuro-retinitis. But even those such as Volhard and Fishberg and Oppenheimer, who maintain the essentially ischemic origin of neuro-retinitis, consider that choked discs in hypertension are usually to be ascribed to raised intracranial pressure.

In discussing the pathogenesis of the retinal lesions in hypertension, we must not lose sight of the essential issue, namely the factor which is responsible for the difference between the so-called albuminuric and arteriosclerotic forms of retinitis, for it is not merely the presence of retinal "exudates" which distinguishes malignant from benign hypertension, it is their fluffy character and the presence of bilateral papilledema. I am quite prepared to admit that the retinal exudates and hemorrhages in hypertension are most probably due to local ischemia resulting either from organic or functional narrowing of the arteries concerned. This explanation applies equally to the focal retinal lesions found in benign and malignant hypertension which lesions Moore (12) considered to be similar in their histological appearances, and it entirely fails to account for the essential difference between the two retinal pictures; it is indeed unfortunate that so few of the upholders of the purely ischemic theory have directed their thoughts to this issue. In 1934 I published the results of cerebrospinal fluid pressure measurement in 37 cases of hypertension (13). In this series it was found that 12 patients with a cerebrospinal fluid pressure of 250 mm. of water or more presented albuminuric retinitis, or subsequently developed it, while 20 out of 21 patients with lower pressures either had no retinal lesion other than arteriosclerosis, or had the retinal appearances of arteriosclerotic retinitis; three patients provided an intermediate group in which the cerebrospinal fluid pressure was sometimes above and sometimes below the critical level. As a result of these determinations I suggested that the differences between hypertensive neuro-retinitis and arteriosclerotic retinitis were due to the presence in the former and the absence in the latter of an intracranial pressure sufficiently high to cause accumulation of fluid in the nerve-head and retina. In its full form this hypothesis supposes that in the two forms of retinitis, the "exudates" and hemorrhages have a similar origin, probably a local circulatory disturbance, but that in neuro-retinitis the changes of neuro-retinal edema are added as a consequence of the level of intracranial pressure. Some objections have been raised to this hypothesis. Thus Fishberg (6) states that he has encountered cases with neuro-retinitis in which the cerebrospinal fluid pressure was not raised. I published one such case and I have subsequently met others; the fact therefore is not disputed. But I would point out that the same is

true in tumor of the brain (1), where it is not very rare to find papilledema in the presence of a normal or only slightly raised cerebrospinal fluid pressure, and where nevertheless it is generally agreed that papilledema is the result of raised intracranial pressure. Again it has been argued that the cerebrospinal fluid pressure becomes raised in congestive cardiac failure and in obstruction of the superior vena cava without the development of neuro-retinal edema. This also is true; in one recent case of bronchial carcinoma obstructing the superior vena cava, the brachial venous pressure was raised by 30 cm. and the cerebrospinal fluid pressure was 42 cm. but papilledema was absent. It seems clear that when the venous pressure is raised throughout the head and neck, papilledema does not occur; it only occurs when there is a rise of intracranial pressure due to an intracranial abnormality. I cannot therefore accept these objections as disproving the validity of the hypothesis presented, which seems the only one offering an adequate explanation of the differences between the retinal pictures found in benign and malignant hypertension. In my series I could only find one variant clearly related to the cerebrospinal fluid pressure, namely the diastolic arterial pressure, and accepting a causal relationship between the two it seems more likely that arterial determines cerebrospinal pressure than vice-versa, but it is not at present clear how this relationship is effected. Now the diastolic arterial pressure is the best simple index of the degree to which the peripheral resistance is increased during hypertension; for the systolic is greatly influenced by the elasticity of the great vessels. And thus it seems that raised intracranial pressure, the factor which determines the retinal picture of malignant as contrasted with benign hypertension, is a consequence of the severity of the hypertension.

In 1938 Goldblatt (9) reported that severe constriction of the renal arteries in dogs might produce a condition resembling malignant hypertension in presenting gross hypertension, hemorrhages into the gut and progressive renal failure during life, and arteriolar necrosis in many organs, but not in the clamped kidney, after death. All Goldblatt's animals presenting arteriolar necrosis had both grossly raised arterial pressure and renal failure, and since he never observed arterial changes in animals with only one of these factors present he concluded that both were involved in the production of the lesions. Shortly afterwards, and independently, Wilson and I (19) reported acute arteriolar necrosis and endarteritis in rabbits in which Prinzmetal and I had produced hypertension by a modification of Goldblatt's method. These lesions were found chiefly in the gut, but also in liver, suprarenal heart and eye; and since they were absent in the kidney whose renal artery had been clamped, and they only developed in animals presenting grosser degrees of hypertension, we inferred that a grossly raised intravascular pressure was the chief factor in their causation. The crucial test of this hypothesis could not be made in the rabbit because in this animal it is impossible to produce gross hypertension

by constricting one renal artery while the other kidney remains normal. This experiment was carried out in the rat by Byrom and Wilson (20, 21) and the results have proved most illuminating. They found that arteriolar necrosis developed in the intact but not in the clamped kidney of animals with hypertension, a finding which establishes the essential rôle of the intravascular pressure in the pathogenesis of the lesions. They showed further that the arteriolar and parenchymal lesions in the unclamped kidney both in their acute and more chronic stages duplicated the changes found in malignant hypertension in man. Finally they have found that when these changes have developed in the unclamped kidney, hypertension may persist after removal of the clamped kidney, and they interpret this as demonstrating that these lesions interfere with the blood flow through the kidney and thus contribute to the maintenance and intensification of the hypertension. In other words, malignant hypertension is a vicious circle, a gross hypertension producing renal arteriolar necroses which further intensify the hypertension through the renal ischemia they produce.

Volhard originally pointed out that the diastolic pressure is usually higher in malignant than in benign hypertension, and this has been the experience of subsequent writers; thus it is unusual to find the diastolic pressure under 130 mm. Hg. in malignant, or above it in benign hypertension. The hypertension is thus in general more severe in the malignant than in the benign form and it is this difference in severity which, as has been pointed out, accounts for the chief differences between them. While the hypertension thus differs in degree, does it also differ in kind? Volhard (16, 17) has divided hypertension into two forms, pale hypertension which includes nephritic and malignant hypertension, and some less common varieties, and red hypertension which is synonymous with benign hypertension. In the former he supposes that the hypertension is due to the release from the kidney of a pressor substance, while in the latter it is due to changes in elasticity of the arteries and arterioles, but the supporting evidence which his pupils adduced has not been confirmed. He supposed that in malignant hypertension arterial constriction in the kidney led to arteriolar necrosis, and the resultant ischemia intensified the hypertension; thus there would exist a vicious circle, for which Wilson and Byrom have produced evidence, though their explanation differs in detail from that conceived by Volhard. The view is now widely held that in benign hypertension the raised pressure is also renal in origin, but the evidence on which this view is based is still equivocal. At the present time one can say that it is unnecessary to suppose that the hypertension differs in kind in the benign and malignant forms, though no final conclusion can be drawn until the mechanism whereby the pressure is raised has been conclusively demonstrated in man.

The conception of the relationship of benign and malignant hypertension here developed allows us to see some other facts in their true perspective.

What we call malignant hypertension frequently develops in patients initially presenting a condition indistinguishable from benign hypertension in which the causal lesion is not accurately known; it may also occur in chronic pyelonephritis and in Cushing's syndrome; finally cases of true chronic nephritis in its terminal stages present a somewhat similar clinical picture and at post-mortem examination may show arteriolar necrosis. The hypertension may also follow the benign course in chronic pyelonephritis and in Cushing's syndrome, and in some cases of slowly progressive chronic nephritis albuminuric retinitis is not found in life nor arteriolar necrosis after death. Thus we see, on the one hand, that the causal lesion is not always the same in malignant hypertension, and, on the other, that a given kind of lesion may be accompanied by a hypertension which follows either the benign or the malignant course. These features are readily explained on the view that the benign and malignant courses of hypertension are merely expressive of the severity of the hypertensive process, irrespective of the lesion which ultimately determines it.

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LUNG ABSCESS

REPORT OF A CASE WITH UNUSUAL ONSET AND COURSE

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In arriving at a diagnosis of lung abscess, one invariably searches for an etiological factor to fit each individual case. According to Wessler (1) these causative factors are the various forms of pneumonia: aspiration of foreign bodies, often while the patient is stuporous or unconscious; post-operative (either local operations on the nose or throat or abdominal surgical procedures); perforating chest wounds; metastatic, as in general blood infections; empyema; and neoplasms, tuberculosis, bronchiectases, actinomycosis, diabetes, syphilis and perforated carcinoma of the esophagus. The aspiration type of abscess more often affects the upper lobes, while in the other forms the lower lobes are more often involved. In most instances the course of the abscess can be traced from its supposed etiology to its formation. The case herein reported appears to differ from others, inasmuch as the cause is by no means clear and the mode of onset and course unique.

CASE REPORT

History (Adm. 471710). P. L., a male, aged 58, a plumber by occupation, was first taken ill on April 1, 1941. The onset was sudden with sharp sticking pain in the left hypochondrium, radiating to the epigastrium and from this point to the back. Severe nausea, weakness and sweating were concomitant symptoms, following which the patient had marked cardiac palpitation. A hypodermic injection of morphine was administered and in about one hour the pain subsided. The following day the temperature was 101°F., the nausea persisted, but there was no vomiting. Tenderness and dull pain were present in the left hypochondrium for two days. From the physician who attended the patient during this attack it was learned that there were no physical signs in the chest, and the only abdominal finding was the tenderness in the left hypochondrium. The symptoms subsided completely in three days and as there was no further temperature elevation, the patient was allowed to be out of bed. He felt weak and his appetite was poor, but he had no pain, no cough or difficulty in breathing. For the next eight days he was symptom-free.

I saw the patient for the first time on the evening of April 8, 1941. He had again experienced sharp pain in the left hypochondrium, nausea, sweating and a sensation of general collapse. The clinical picture at this time resembled closely that seen in acute coronary thrombosis. The patient was pale, covered with cold perspiration and in a state of circulatory collapse. The pulse was rapid (114 per minute) and thready and the respiratory rate was 28 per minute, regular and shallow. Examination of the chest showed only a few fine râles at both bases. The heart action was rapid and feeble. There were no murmurs and the heart was not enlarged. The

upper half of the abdomen was rigid and there was marked tenderness in the epigastrium and right hypochondrium. There was no free fluid in the abdomen. The reflexes were normal and there was no edema of the extremities. Owing to the critical condition of the patient no detailed history could be obtained at the time. The urine was clear, had a specific gravity of 1018, showed a faint trace of albumin, no sugar and an occasional granular cast. Blood examination showed a white count of 18,000 with 79 per cent polymorphonuclear leucocytes, 20 per cent small lymphocytes and 1 per cent eosinophiles. The blood pressure was 110 systolic and 80 diastolic, and the temperature 99°F. The tentative diagnoses made at the time were coronary thrombosis or an attack of pancreatitis. Morphine sulfate (gr. ss in two doses of $\frac{1}{4}$ grain each) was administered and the patient spent a comfortable night. The next morning his general condition was better, the pulse slower and fuller, but the temperature had risen to 102°F. Examination of the chest revealed numerous moist râles over the left lower lobe, but no signs of consolidation. The upper abdomen was still rigid and the tenderness in the left hypochondrium persisted. The white blood count had risen to 21,000 and the polymorphonuclear count to 82 per cent of which the segmented forms constituted 49 per cent and the non-segmented 33 per cent. An electrocardiogram taken on this day showed no abnormalities. The patient was able to give a history and stated that he had never been ill up to the time of the first attack, nine days previously. He had never had a cough or any symptoms related to his gastro-intestinal or genito-urinary tract. His bowels were always regular. His habits as to diet, coffee, tobacco, and alcohol were very moderate. He stated that on March 26, 1941 he had fallen from a ladder and that a steel file that he held in his hand had struck his left chest, but had not caused a flesh wound. He had pain in the left chest for two hours after the accident and a slight cough and thought that he raised a slight amount of blood-streaked sputum which he attributed to bleeding from his teeth, which might have been struck during the fall.

Thinking that he was developing a process in his left lower lobe he was given one gram of sulfathiazole every four hours.

The following day his condition was worse. The temperature had risen to 103°F. and there were signs of fluid in the left chest. Dyspnea and cyanosis were marked. Hospitalization was advised.

After admission to the hospital it was noted that the fluid in the left chest was accumulating rapidly, as was evidenced by the dislocation of the heart and trachea to the right. X-ray examination of the chest showed a large accumulation of fluid extending from the base to the angle of the scapula on the left side. Aspiration revealed bloody fluid of which 150 cc. were withdrawn. It was then assumed that we were dealing with a pulmonary neoplasm which had ruptured into the pleura. Examination of the fluid showed no bacteria and no tumor cells. X-ray examination of the chest the following day showed a decreased amount of fluid. The patient's temperature kept at a level of 102°F. and the white blood count was 17,000 with 82 per cent polymorphonuclear leucocytes. The following day the fluid had risen to the spine of the scapula and aspiration gave 200 cc. of thick bloody fluid, the examination of which again showed no tumor cells, but the presence of streptococcus viridans. The patient continued to run a fever between 102° and 103°F. and developed a severe cough with thin, odorless, mucoid expectoration. Examination of the sputum for tubercle bacilli was negative. The chest filled up within twenty-four hours after it had been partially emptied. Further x-ray examinations showed several loculated collections of fluid and marked increase in size of the right hilum. A diagnosis of metastatic neoplasm was ventured on this finding by the x-ray department (Dr. M. Sussman).

On April 29, 1941 signs of a localized pneumothorax were made out in the left axillary region. A needle was inserted in the fifth interspace in the anterior axillary line

and pointed upward and inward. No fluid was obtained, but it was noted that the piston of the syringe was pushed upward, undoubtedly due to the positive intrapleural pressure. When the syringe was withdrawn the odor of the gas in the syringe was noted to be extremely foul. It was concluded that we were dealing with a ruptured lung abscess, causing the hemothorax and immediate operation was advised.

The patient was operated by Dr. Arthur Touroff the same evening. A left axillary incision over the sixth rib was made; $3\frac{1}{2}$ inches of rib resected and edematous thick parietal pleura found. Aspiration yielded thick foul pus. The pleura was incised and 1 litre of pus evacuated by suction. Just below the incision the bronchial fistula leading into a small abscess cavity was found. This was drained and the cavity packed. The patient suffered somewhat from shock and immediately after the operation his temperature fell to 96°F. However, he made a rapid recovery and was discharged from the hospital one month after the operation.

SUMMARY

1. A case of lung abscess with loculated empyema possibly caused by trauma to the chest wall without a perforating wound, but with a possible deep hematoma.

2. The unusual finding of the foul gas without pus led to the correct diagnosis.

REFERENCE

- (1) WESSLER, H.: Lung abscess and Bronchiectasis. *Am. J. Roentgenol.*, 6: 161-174, 1919.

POSTOPERATIVE PRECIPITATION OF VITAMIN B COMPLEX DEFICIENCIES

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The nutritional history of patients with chronic digestive disturbances requiring surgical therapy is often marked by the development of numerous inadequacies of vital food factors. In the first place these chronic illnesses are often associated with anorexia and not infrequently with vomiting. The nature of the illness may itself occasion a therapeutic restriction of diet, such as the low residue or bland diet.

In the second place the pre-operative preparation of the patient involves a sharply limited diet, especially when surgery of the gastro-intestinal tract is contemplated. The administration of quantities of fluids by mouth and intravenously provides the added effect of induced diuresis whereby the excretion of water soluble vitamins is increased. Parenterally given fluids usually contain glucose. The drain on the vitamin economy of such a high carbohydrate intake has been recognized for a long time.

The third important consideration is the operation itself. The insult of operative trauma as well as the deleterious effect on the liver and other organs of prolonged anesthesia, tend to disrupt the mechanism of action of vitamins.

A fourth factor is the postoperative period. Here one encounters post-anesthetic nausea and vomiting. In addition the necessity often arises for complete restriction of foods as after partial or total gastrectomy. Fluid balance is maintained by the continued use of intravenous fluids which contain glucose. All these factors add up on the debit side of nutritional balance.

With these factors in mind a study was made of a number of actual cases. Daily rounds were made on one male surgical ward of thirty-eight beds at The Mount Sinai Hospital. The patients, admitted routinely, were typical of an active surgical service of a general hospital. Within the short space of one month, nine patients were diagnosed as having a deficiency state with respect to one or more components of the vitamin B complex. The clinical histories, in summary, are as follows:

CASE REPORTS

Case 1. History (Adm. 457504). M. B., a 55 year old white man with a known peptic ulcer, had been on a modified ulcer regime for one year, with persistence of

pain and anorexia. Symptoms of obstruction led to his admission for surgical relief. Pre-operatively he was treated with gastric lavages twice daily for two weeks. Each day for one week before operation he received an intravenous infusion of 1500 cc. of 5 per cent glucose in saline. Under general anesthesia, sub-total gastrectomy was performed. Postoperatively he received a continuous infusion of 5 per cent glucose in saline. His course was marked by the development of a duodenal leak, pneumonia and urinary retention. He was given 10 mg. of thiamin chloride and 100 mg. of cevitamic acid daily.

Two weeks after operation he complained of burning of the tongue. The tongue was red, smooth, dry, and had a glazed appearance; a few areas showed a contrasting heavy furring. He was given 500 mg. of nicotinic acid each day, orally, in five divided doses. Symptoms and objective findings began to clear dramatically within 24 hours and had completely subsided in 5 days. Nicotinic acid was continued throughout the rest of his convalescence; there was no recurrence.

Case 2. History (Adm. 458816). G. W., an octogenarian, was admitted for progressive symptoms of urinary obstruction which gradually became complete. Throughout this period, which was somewhat more than a year, he had marked anorexia. In addition to the indicated urological therapy for vesical calculus and hypertrophied prostate, he was given 10 mg. of thiamin chloride, 100 mg. of cevitamic acid and 100 mg. of nicotinic acid daily, by mouth.

Two weeks after admission, at which time his blood urea nitrogen was 11 mg. per cent, he was noted to be torpid, unresponsive and dysarthric; he was confused and disoriented; he perseverated in speech and had visual hallucinations. The neurological examination was negative, except for a generalized tremor. His tongue was beefy red, glazed, and swollen and interfered with cleansing measures in the mouth. He complained of burning of the tongue. The dosage of nicotinic acid was immediately increased to 400 mg. daily, in four divided doses. His appetite improved remarkably. Four days later his tongue was of normal size and contour and the burning had disappeared. There could now be seen a deep magenta color of the tongue, as well as seborrhea-like lesions in the naso-labial folds, suggestive of a riboflavin deficiency. Three days after this observation the normal landmarks and papillae of the tongue were all present, and no pathological findings were visible. The lesions suggestive of ariboflavinosis also disappeared, presumably due to the increased riboflavin intake, concomitant with the increase in food intake.

Two weeks later, a suprapubic cystostomy was performed, and the postoperative course was uneventful. Vitamin therapy in the last named doses was continued and no deficiency lesions developed.

Of especial interest here are the secondary appearance of lesions suggestive of ariboflavinosis which cleared with continued improvement of appetite and food-intake, also the development of a nicotinic acid deficiency syndrome in spite of the prophylactic use of 100 mg. of this vitamin daily by mouth.

Case 3. History (Adm. 459118). J. C., a 68 year old man developed urinary difficulties one year before admission as a result of an old urethral stricture. Intermittent febrile episodes and progressive anorexia characterized the clinical course. He was admitted because of urinary extravasation. Under general anesthesia, the extravasation was drained and a supra-pubic cystostomy was performed. For ten days postoperatively he was given a continuous infusion of 5 per cent glucose in saline. In addition, sulfanilamide was administered.

Eight days postoperatively, the nursing staff noted unusual difficulty in maintaining oral hygiene. His tongue now was thickened, smooth, red and glazed. Its surface was marked by many fissures and a few scattered vesicles. The lips were dry,

pale, and macerated. There was a moderate degree of seborrhea along the alae nasi. Definite roughening was felt on the skin of the dorsum of the hands. There was no calf tenderness.

Riboflavin concentrate, the equivalent of 40 mg., three times daily, was prescribed. In two days his lips had improved markedly. His tongue appeared less angry red. In five days his lips cleared completely. The tongue continued to improve and it was felt that this improvement could be at least partially related to increased intake of nicotinic acid, since there was a striking improvement in his appetite and food intake. Because of the relatively slower tempo of clearing of the smoothness of the tongue, he was given 500 mg. of nicotinic acid orally each day. This removed effectively all traces of tongue abnormality. Unfortunately, this patient later developed bilateral pyelonephritis and bronchopneumonia and eventually succumbed.

Case 4. History (Adm. 458933). J. P., a 40 year old man, had had an appendectomy 16 years prior to admission, followed by an anastomotic operation for small intestinal obstruction 6 years later. Since then he had suffered from dyspeptic symptoms which he learned to relieve by a soft, low-residue diet. He was admitted to the hospital and operated on for a perforated peptic ulcer. Postoperatively a Levin tube was inserted into the stomach and a continuous infusion of 5 per cent glucose in saline was administered intravenously for a prolonged period.

Two days later he complained of burning tongue and soreness of the mouth which persisted in spite of the local application of mineral oil, frequent mouth washes, and careful oral hygiene. The tongue was enlarged and thickened; there was an uneven coating with intervening smooth patches of red, and a few small fissures. He was given 300 mg. of nicotinic acid intravenously in 3 divided doses for 4 days. Within 24 hours there was a definite improvement and in 2 days the tongue was practically normal. The therapy was then continued orally.

Case 5. History (Adm. 459673). J. B., a 42 year old man, developed symptoms of acute cholecystitis 7 weeks before admission, which had not subsided completely when he entered the hospital. During this seven week period he voluntarily limited his diet to low residue foods with almost complete abstinence from meats. He lost 7 pounds in weight. In the hospital, a cholecystectomy and a choledochostomy were performed for subacute cholecystitis with cholelithiasis and cholangitis. Postoperatively he complained of abdominal pain, had marked anorexia, and ran a febrile course. Two months after his first operation he was again explored and a common duct calculus was found and removed. For one week postoperatively a continuous intravenous infusion of 5 per cent glucose in saline was maintained. Fever and anorexia persisted; three weeks later a third operation was performed and 1000 cc. of bile-stained pus was removed from a subphrenic abscess. Again an intravenous infusion of 5 per cent glucose in saline was administered.

One week before his last operation (five months following the onset of his illness), he complained of a "taste of bile" in his mouth. From then on, he complained intermittently of burning, soreness, and numbness of the tongue, as well as difficulty in swallowing. Two days before his third operation it was noted that his tongue was beefy red, fissured, and very tender. He stated that in addition to anorexia, he was unable to eat much because of the pain produced in his tongue by any foreign substance in his mouth. There were no clinical evidences of any other vitamin deficiencies. The tourniquet test was negative. He was given 100 mg. of nicotinic acid intravenously and the next morning the swelling of his tongue had considerably diminished, his appetite had increased, and he ate with relative comfort for the first time in days. Nicotinic acid was then administered in 5 doses daily of 100 mg. each

throughout his postoperative period, until complete convalescence. The tongue reverted to a perfectly normal state and has remained so.

Case 6. History (Adm. 458612). K. U., a 76 year old man, had a history of epigastric pain, anorexia, and weight loss for a period of two and one-half years. During the year preceding admission, the symptoms had become progressively more marked, with severe anorexia and constipation. During the week preceding admission there were frequent, intermittent cramp-like pains and repeated vomiting. On admission he had classical manifestations of an obstructive lesion of the transverse colon, the presence of which was confirmed by a barium enema. He was immediately given a continuous intravenous infusion of 5 per cent glucose in saline and a Levin tube was left indwelling. Four days later, under general anesthesia, the malignant tumor was removed, and a temporary colostomy established. The intravenous infusion was maintained for 5 days postoperatively. One week after operation he was started on a soft, low residue diet.

The nurses' records at this time made note of the fact that in spite of frequently repeated, painstaking oral hygiene, the patient complained of pain in the mouth; in addition he had foul odor of the breath. The pain became rapidly worse and any attempt at eating or drinking resulted in such marked discomfort that the patient went on a "hunger strike." His mental state changed so that he became uncooperative, disoriented at times, and confused. The dentist who saw him noted poor oral hygiene and flat, light tan colored serpiginous patches with a red border distributed over the mucosa of the lips, cheeks, vestibule, hard palate, facies and gingivae. He was treated locally with gentian violet. The lesions, however, progressed so that two days later, there were also present ulcers and bullae of the oral mucous membrane. He complained bitterly of burning in the mouth and refused even water. His condition declined rapidly. The tourniquet test was negative and there was no bleeding tendency. There was no evidence of peripheral neuropathy and he had no eye symptoms.

For purposes of control he was started on riboflavin 10 mg. three times a day. After twenty-four hours there was still further extension of the oral lesions. Therefore, the patient was treated with 300 mg. of nicotinic acid, administered intravenously, in three divided doses. There ensued at once a dramatic change. Overnight there was a marked decrease in his symptoms. He began to eat and his mental state cleared rapidly. Objectively, within twenty-four hours, the angry, grayish slough overlying the ulcers cleared considerably; within five days the lesions had entirely cleared. The patient's appetite improved markedly, and within two weeks he had gained sufficient strength to permit the surgeons to proceed with the closure of his colostomy. During this second operative period vitamin therapy was maintained. There was no recurrence.

We feel that this man's life was saved by the institution of specific vitamin therapy.

Case 7. History (Adm. 463644). A 34 year old dental mechanic entered the hospital because of massive gastrointestinal hemorrhage manifested by tarry stool, dizziness and weakness. Two years previously he had had a similar episode of severe hematemesis and melena. Examination then led to the diagnosis of Banti's syndrome with splenomegaly and bleeding esophageal varices. Splenectomy was advised and performed on this, his second admission.

His therapy in the hospital consisted of the following measures: when he was first admitted he was given a transfusion and then kept on a continuous intravenous infusion of 5 per cent glucose in saline. A soft diet was given throughout his stay. After three weeks of hospitalization he went home for two weeks to arrange his

affairs and then returned for the splenectomy. Following the operation he ran persistent fever as high as 102°F. for many weeks. On the ninth day after operation a complete dehiscence of the wound developed with protrusion of numerous loops of small intestine and omentum. Secondary suture was performed and sulfanilamide administered. A continuous intravenous infusion of 5 per cent glucose in saline, such as had been given immediately prior to and following the operation, was again started and continued for five days. All this time he was held to a low residue, bland diet. Two weeks postoperatively he was given 100 mg. of nicotinic acid, 100 mg. of ascorbic acid, and 5 mg. of thiamin chloride, each three times a day. For the next week he complained of uncomfortable sensations in the mouth and was given sodium perborate mouth washes with little relief.

He was seen by us one month following the operation at which time he presented the syndrome now recognized to be that of ariboflavinosis: his tongue was of a deep magenta color and somewhat smooth at the edges, and without the fiery redness of nicotinic acid deficiency. Cheilosis with slight, superficial fissuring at the angles of the mouth was also present. In addition, his gums were noted to be purplish in color, heaped-up and edematous, although not tender. He was started on riboflavin concentrate, equivalent to 6 mg. of crystalline vitamin B₂, three times daily. Before starting therapy, the patient had begun to have a marked increase in appetite resulting in a much larger consumption of food. However, with the administration of riboflavin there was a prompt disappearance of the cheilosis and of the characteristic magenta color of the tongue. The gums also rapidly receded to a normal state.

This case is of especial interest in that a patient who was given vitamin B₁, vitamin C and nicotinic acid in large doses, developed an isolated, clear-cut riboflavin deficiency which responded to specific therapy. Especial attention is drawn to the appearance of the gums, as we have observed this to be one of the earliest and most characteristic signs of avitaminosis as manifested in the mouth.

Case 8. History (Adm. 462350). A 71 year old man had been having urinary difficulties for six years. The symptoms had become progressively worse, so that episodes of retention had occurred. He would relieve the retention by self-catheterization. For several months prior to admission his appetite had been poor, and his food intake correspondingly low. On examination in the hospital, in addition to his large prostate and distended bladder, he was found to be emaciated and to have a swollen red tongue.

Bilateral vasectomy and suprapubic cystotomy, were done at once. Three weeks after admission a second stage prostatectomy was done and he was given a continuous intravenous infusion of 5 per cent glucose in saline. One month after admission he was started on 10 minims of viosterol and 10 mg. of vitamin B₁, each twice daily, as well as 4 daily doses of 100 mg. of vitamin C.

Five weeks after admission his tongue was noted to be fiery red, smooth, and glazed. Small ulcerations were also present on its surface. He complained of marked dryness of the mouth. Therapy, unfortunately, was not started until one week later by which time he had developed a right-sided parotitis. He was then started on riboflavin and nicotinic acid in large doses, but his condition declined rapidly, and he died shortly after the onset of the parotitis.

This case illustrates the need for early recognition of these lesions and prompt institution of appropriate therapy. It lends further support to our impression that at least some of the cases of postoperative parotitis that one encounters are directly caused by avitaminosis B. The mechanism would appear to lie in ulceration of the buccal mucous membrane and coincidentally of the mucosa localized within the papilla of Stenson's duct.

Case 9. History (Adm. 453047). A. A. was a known diabetic of mild degree who had a 13 year history of peptic ulcer. Since then he had followed a modified dietary regime for ulcer supplemented by the use of alkali therapy. Four years prior to admission a gastroenterostomy was performed. Two and one-half years later, because of persistent pain and recurring bleeding, a pyloric exclusion operation was done. He reentered the hospital now because of recurrence of pain and tarry stools. X-ray examination confirmed the clinical impression of a jejunal ulcer. He was treated with continuous milk drip and alkali therapy, and because of gastric retention, a gastric lavage was performed twice a day.

This patient was seen by us two days pre-operatively, at which time his tongue appeared red, thickened, and smooth. He complained of burning of the tongue. He was immediately started on vitamin therapy which included 300 mg. of nicotinic acid, 100 mg. of cevitamic acid, 30 mg. of thiamin hydrochloride, and 18 tablets of brewer's yeast daily, in divided doses. The oral manifestations quickly cleared. He underwent a secondary subtotal gastrectomy and jejuno-jejunostomy. Post-operatively he was given a continuous intravenous infusion of 5 per cent glucose in saline for seven days. Vitamin therapy was continued in the above-stated dosage. The patient had no recurrences of his oral manifestations.

DISCUSSION

The clinical manifestations of vitamin deficiencies can be roughly classified into two divisions. In one are the chronic insufficiencies which develop over a long period of time; these are the most common. In the other group are cases presenting the phenomena of a clinically manifest deficiency state which has been precipitated acutely. The latter type is seen in patients who have had a prolonged period of minimal vitamin intake sufficient to prevent clinical symptoms under ordinary circumstances, but insufficient to supply the necessary reserve for a sudden increase in metabolic demands. By the very nature of the differences of these two groups, the symptomatology of the lesions would be expected to differ. Our cases fall into the latter category.

It is not the purpose of this discussion to suggest that all pre-operative or postoperative patients be given "shot-gun" mixtures of the known vitamins promiscuously, but rather to point out the necessity for specific therapy where definitely indicated.

The deficiencies observed in these patients were apparently related to the vitamin B complex alone. Their overt symptomatology was specifically characteristic of nicotinic acid and riboflavin insufficiencies. It must be assumed, however, that deficiencies of other members of the vitamin B complex whose specific syndromes are not yet recognized may have also existed. The symptoms common to most of these patients were anorexia, burning tongue, general malaise, and unrest. The signs included mental confusion or apathy, cheilosis, angular stomatitis, bullous and ulcerative lesions of the oral mucous membrane and tongue, and a smooth, red, beefy, glazed tongue. When riboflavin deficiency predominated one observed a typical magenta-color of the tongue, purplish cyanosis and edematous hypertrophy of the gingival tissue, especially marked in the interdental

delta, and aural and malar seborrhea. It is important to note that none of these patients presented diarrhea and only one showed mild changes of the skin on the dorsum of the hands. No conjunctival or corneal changes were observed, but most of our patients were too ill to permit slit-lamp examinations. Neuritic manifestations were absent in this series. Tourniquet tests revealed no abnormality indicative of increased capillary fragility. Postoperative bleeding was not observed in any of these patients. None of the skin or eye manifestations usually associated with vitamin A deficiency were observed.

These findings lead one to a conclusion the importance of which is greater than the subject under immediate discussion. The food intake of these patients with chronic prolonged illness leading to major surgery is all too frequently deficient in the vitamin B complex, but apparently contains adequate amounts of the other vitamins. The foods which these people most often omit from their diet are the whole grain products, parenchymatous organs, rare cooked meats, raw fruits, leguminous vegetables because of the resulting tendency to abdominal distension, and nuts for the same reason as well as for economy. The elimination of these foods removes the major possible supply of the vitamin B complex.

The importance of these findings is reflected in two ways: 1) in the mortality rate; and 2) in the time required for convalescence. There is no question about the fact that at least one of these patients (Case 6) would have died had he not received specific therapy; we feel that Case 8 may well have been saved had therapy been instituted at an early stage. While it is difficult to estimate the saving in time required for convalescence, the subjective sense of well being and the enormous increase in appetite which immediately followed the therapy were definite demonstration in this limited group of cases of the conversion of a failing patient into a rapidly convalescent one.

The most satisfactory and logical form of therapy is prophylactic. In the pre-operative preparation of this type of patient close attention should be paid to the nutritional status. When the history indicates a prolonged period of restricted diet, special efforts should be made to determine which articles of food have been omitted. The pre-operative examination should include a careful inspection of the lips, gums, tongue, and oral mucous membrane in order to detect the possible presence of deficiency states.

The nature of the illness of many of these patients precludes intensive oral therapy. The question of the ability of the gastro-intestinal tract to absorb the vitamins under certain conditions must also be considered. In this connection, reference should be made to Case 2 in which the full blown oral syndrome of nicotinic acid deficiency developed in spite of the administration of 100 mgs. daily *per os* for 10 days. In addition attention should be called to the incompleteness of therapy when a limited number of components of the vitamin B complex are given as in Case 7 in which the

patient received nicotinic acid, vitamins B₁ and C, yet developed a classical picture of ariboflavinosis, which responded to riboflavin. In other words, the whole vitamin B complex fortified by nicotinic acid and riboflavin should be administered. Where oral therapy is not possible, the parenteral routes should be used.

Therapy directed toward the relief of acute symptoms must of course be intensive. Three hundred milligrams of nicotinic acid daily, given intravenously in divided doses, is adequate, in our experience, to relieve the symptoms within forty-eight hours. Fifteen milligrams a day of riboflavin by mouth is a sufficiently large dose of this component. Liver extract intramuscularly will supply the rest of the members of the vitamin B complex. As soon as the patient is able to eat a full diet, these supplementary vitamins may be discontinued.

A QUANTITATIVE METHOD FOR DETERMINING COLLATERAL CORONARY CIRCULATION¹

PRELIMINARY REPORT ON NORMAL HUMAN HEARTS

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Numerous studies have been made on the collateral circulation of the heart. It is the purpose of this study to investigate two important questions. First, does collateral circulation exist between the right and left coronary arteries of the normal human heart? Second, if such channels exist, what is the volume of blood which can be carried by these collateral vessels?

Regarding the first question, two separate opinions seem to be prevalent. First, Gross (4) and Spalteholz (6) believed that anastomotic vessels are not present normally in youth and developed normally only with age. On the other hand, Blumgart, Schlesinger, and Davis (1) in a very extensive and comprehensive study believed that normally no effective collateral circulation exists in the normal heart regardless of age, but only develops if cardiac disease, especially coronary artery disease, is present.

Regarding the second question, that is, the volume of the collateral circulation, if such exists, nothing seems to be known. Various substances such as gelatin, agar, celloidin, waxes, starches, dyes and metals (7) have been injected into one coronary artery and attempts were made to see if any of these entered the other coronary artery. Occasionally, some of the injected material has been found in the opposite vessel. Such observations give no information whatsoever of the percentage of blood that can flow from one side to the opposite. It is only by knowing the volume of blood in terms of percentages of total coronary flow that the relative effectiveness of such flow can be understood. It may be pointed out that all of the numerous studies on this subject have been qualitative and none quantitative.

We have attempted to answer these questions in the normal heart by means of a modification of Dock's ingenious kerosene perfusion method (3). In earlier efforts the measurement of flow through the coronary arteries by means of perfusion was inaccurate because of the rapid onset

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of edema of the vascular walls, which progressively interfered with the circulation. Dock conceived the idea of perfusing the heart with a fluid which did not collect in the tissue spaces of the vessel wall and cause edema. He chose kerosene for this purpose and has already added substantially to our knowledge of blood flow in normal and hypertrophied hearts (3). He has also applied this method to the kidney (2). Dock kindly demonstrated his method to us and we desire to take this opportunity to thank him.

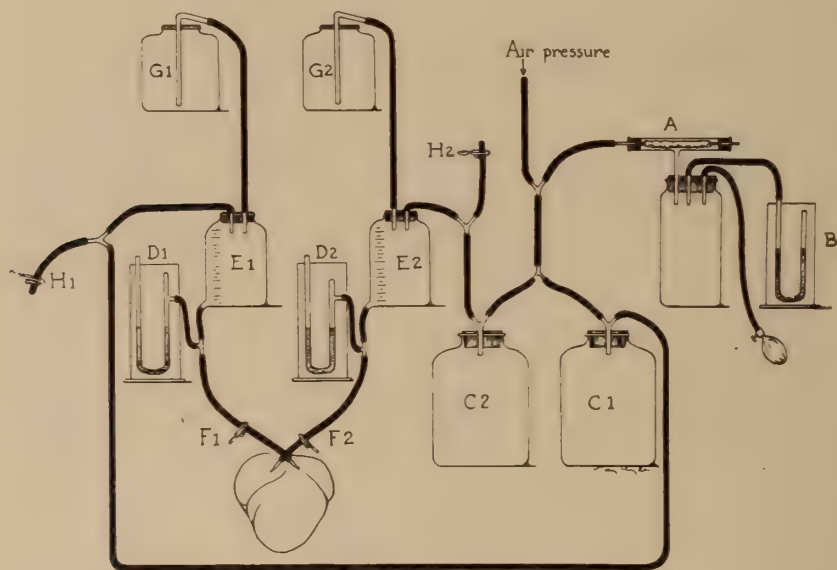


FIG. 1. Diagram of perfusion apparatus

A, Starling valve.

B, Mercury manometer.

C₁ and C₂, Reservoirs for air under pressure, maintaining an even flow.

D₁ and D₂, Mercury manometers measuring pressure at outlet of perfusion bottles.

E₁ and E₂, Graduated perfusion bottles.

F₁ and F₂, Clamps to stop flow of kerosene.

G₁ and G₂, Reservoirs for excess kerosene.

PRINCIPLE OF METHOD

We have modified Dock's method so that it can be used for the study of collateral circulation of the heart. Briefly, the principle of the method is as follows: Both coronary arteries are cannulated and perfused with kerosene at constant known pressures by means of two separate perfusion systems (fig. 1). The flow through each artery while both are being perfused at the same pressure is measured. One coronary artery is occluded suddenly by clamping the tube proximal to the cannula but the flow through the opposite coronary is not interrupted and is maintained at the same pressure as before. If the flow through the unobstructed vessel increases, it must indicate that new channels are being utilized to allow

more fluid to flow into the heart. Knowing the flow before the opposite vessel was occluded, the increase in flow must necessarily be due to fluid going through the collateral circulation. The percentage of collateral circulation can thus be readily calculated.

DETAILS OF METHOD

Hearts obtained from post-mortem examinations were kept at 4°C. for approximately twenty-four hours and then incubated at 37°C. in normal saline for four hours in order to overcome rigor mortis. Metal cannulae² (largest ones that fit coronary ostiae snugly) were then tied securely in place in the mouths of the right and left coronary arteries after dissecting away the connective tissue around each orifice to insure a secure hold for the suture. Two large clamps were then placed so as to cut off most of the circulation to the auricles; but not to impede or obstruct the coronary circulation of the ventricles or the venous return. A further purpose served by the clamps was to suspend the heart from two ring stands in a vertical plane while the heart was being perfused. In order to allow the perfusion fluid to escape, a small nick was made in the coronary sinus.

Constant pressure was maintained by means of a Starling valve (A), the amount of pressure being determined by a mercury manometer (B) and checked by two mercury manometers (D₁ and D₂) placed between the kerosene perfusion bottles and the mouths of the coronaries, thus checking the pressure practically at the cannulae.

Perfusion bottles were graduated and the time intervals required for a set amount of kerosene to flow into the heart determined by means of stop-watches. In this manner, the rate of flow could be determined for each side independently (by shutting off the opposite perfusion system with a clamp at F) or for each side while the opposite side was being perfused also (no clamp at F). The procedure was then repeated to make sure checks could be obtained. After doing this for both the right and left sides, a calculation could be made as follows:

Total flow = Flow on left plus flow on right.

(with opposite perfusion system in operation; no clamps at F)

Collateral flow = Independent flow (left plus right; with clamps at F) minus total flow.

$$\% \text{ Collateral} = \frac{\text{Collateral flow}}{\text{Total flow}} \times 100$$

Flow on left = Flow on left with opposite perfusion system in operation.

Collateral flow

(left to right) = Flow on left with opposite perfusion system clamped minus flow on left with opposite perfusion system in operation.

² Obtained from Harvard Apparatus Company, Dover, Mass.

Percentage collateral

$$(\text{left to right}) = \frac{\text{Collateral flow (left to right)}}{\text{Flow on left}} \times 100$$

Flow on right = Flow on right with opposite perfusion system in operation.
Collateral flow

(right to left) = Flow on right with opposite perfusion system clamped
minus flow on right with opposite perfusion system in operation.

Percentage collateral

$$(\text{right to left}) = \frac{\text{Collateral flow (right to left)}}{\text{Flow on right}} \times 100$$

As a preliminary, the heart was perfused with one liter of kerosene at 200 mm. Hg to further remove rigor of the vessels and wash out the blood. Thereafter, the perfusion pressure used in most cases was 100 mm. Hg, except in instances of children's hearts when 75 mm. Hg was used or hypertensive hearts, when 150 mm. Hg was the perfusion pressure. Two observ-

Example of procedure

LEFT CORONARY				RIGHT CORONARY			
Pressure	Amt.	Time	Calculated flow per minute	Pressure	Amt.	Time	Calculated flow per minute
<i>mm.</i>	<i>cc.</i>	<i>seconds</i>	<i>cc.</i>	<i>mm.</i>	<i>cc.</i>	<i>seconds</i>	<i>cc.</i>
100	200	28.4	422	100			
100	200	26.8	448	0	(clamp at F ₂)		
100	200	28.	429	100			
100	200	27.2	441	0	(clamp at F ₂)		
100				100	100	30	200
0	(clamp at F ₁)			100	100	27.6	217
100				100	100	30.4	197
0	(clamp at F ₁)			100	100	27.2	220

Total flow = 425.5 cc. + 198.5 cc. = 624 cc. per minute

Collateral flow = (444.5 cc. + 218.5 cc.) - (425.5 cc. + 198.5 cc.) = 39 cc.
per minute

% Collateral = 6.25%

Flow on left = 425.5 cc. per minute

Collateral flow

(left to right) = 444.5 - 425.5 = 19 cc. per minute

Percentage collateral

$$(\text{left to right}) = \frac{19}{425.5} \times 100 = 4.45\%$$

Flow on right = 198.5 cc. per minute

Collateral flow

(right to left) = 218.5 - 198.5 = 20 cc. per minute

Percentage collateral

$$(\text{right to left}) = \frac{20}{198.5} \times 100 = 10.5\%$$

ers were required, one to operate the stop-watch, carefully watching the graduations in the perfusion bottle, and the other to place and remove clamps as directed and to record the time interval indicated on the stop-watch. In order to obtain continuity, two stop-watches were necessary, so that there would be no loss of time from the end of one observation period to the start of the next. The amount timed was usually one graduation or 100 cc., unless the time required was less than ten seconds, in which event, two graduations (200 cc.) were timed.

RESULTS

This procedure was performed on 12 normal hearts. The results are given in table 1. It may be seen, with one exception, that collateral

TABLE 1

AGE	SEX	AMOUNT OF COLLATERAL CIRCULATION	PER CENT COLLATERAL
		cc.	
3	M	5.5	3.2
6	M	21.0	5.6
21	F	53.0	8.6
23	F	28.0	5.4
23	F	21.0	4.6
27	M	37.5	5.2
36	M	0	0
40	F	52.0	5.6
40	F	5.0	0.8
51	F	24.0	5.4
51	F	86.0	5.2
67	M	40.0	6.4

circulation existed between the right and left coronary arteries. The average collateral circulation was 25.4 cc. of blood per minute which was 4.16 per cent of the total coronary blood flow.

In addition to the calculations of the total collateral flow, calculations were made to determine the amount and percentage of collateral flow from the left to the right coronary artery, and from the right to the left coronary artery. In the 12 normal hearts, the average flow from the left to the right coronary artery was 19.2 cc. or 4.55% of the average flow through the left coronary artery; from the right to the left coronary artery the average flow was only 6.2 cc. or 4.05% of the average through the right coronary artery. The reason for the differences between the amount of collateral flow from right to left coronary artery and the left to right coronary artery in the same heart is not obvious. The amounts vary from heart to heart and are not all in the same direction. This difference may be due to imperfections in technique. However, the possibility also

exists that there may be anatomic variations in the communicating vessels branching so that in one direction there is a partial valve-like obstruction caused by this branching.

We do not presume that the values obtained by the kerosene perfusion method are the same as those found during life. However, as Dock (3) has pointed out, they do represent a fair indication of that which exists in the normally beating heart.

We have not performed enough experiments to know whether the collateral circulation is greater in later than in early life, but in five hearts of individuals under the age of twenty-seven the average magnitude of collateral flow was approximately the same as that of the three hearts of individuals dying of conditions other than cardiac disease over the age of forty. If the volume of the collateral circulation increases with age, it seems probable that such increase is not particularly high. Further studies are now being performed to determine quantitatively the changes occurring with age.

X-RAY STUDIES BY A MODIFIED SCHLESINGER METHOD

One of the most significant advances in the study of collateral circulation of the heart was by Schlesinger (5). Schlesinger modified Gross' method in that after injecting the coronary arteries with radiopaque material, the heart was dissected and unrolled so that all the vessels were on one plane, after which the x-ray was taken. This method is of great value in demonstrating the presence or absence of coronary disease. Since it was important for us to be sure that the arteries in our series were normal, Schlesinger's method was adopted but two important modifications were made, which we feel give added information.

1. Schlesinger's lead-agar does not penetrate into all vessels smaller than 40 microns in diameter. This mixture is three times as viscous as blood. Since a great deal of blood can pass through vessels smaller than 40 microns, it was decided to use a radiopaque mixture having physical properties similar to that of blood, which, therefore, would go into the smaller vessels. We consequently used the mixture employed by Dock (3):

Two hundred fifty grams of lead carbonate and 50 gm. mercuric sulfide with 500 cc. water were mixed in a ball mill jar to get a fine suspension (Solution A). Then, to 500 cc. water, 120 gm. sucrose and 60 gm. "Difco" Gelatine were added (Solution B). The latter was warmed to 50°C. with constant shaking. Solutions A and B were then mixed and filtered through two layers of wet cheese cloth and the mixture was placed in the icebox until needed. The mixture was injected directly into the cannulae, making certain that no air was admitted. About 100 cc. of mixture heated to 50°C. was placed in a heavy walled 250 cc. Erlenmeyer flask and injected at 150-200 mm. Hg measuring the pressure with a mercury manometer. After injection the mixture was hardened in an icy saline bath, taking care to turn the heart from side to side to prevent settling on any particular side. After hardening, the injected mass remained hard even at room temperature.

The specific viscosity of this mixture was determined by means of a Saybolt Universal Viscosimeter. It was found to be 5.40 as compared with 4.07 for blood. It is thus apparent that if this mixture, having a viscosity slightly greater than blood, passes through collateral vessels, normal blood should pass through the same channels.

2. At first we injected both arteries and then took x-rays. We used a different dye for each side, but abandoned this because their rapid diffusion

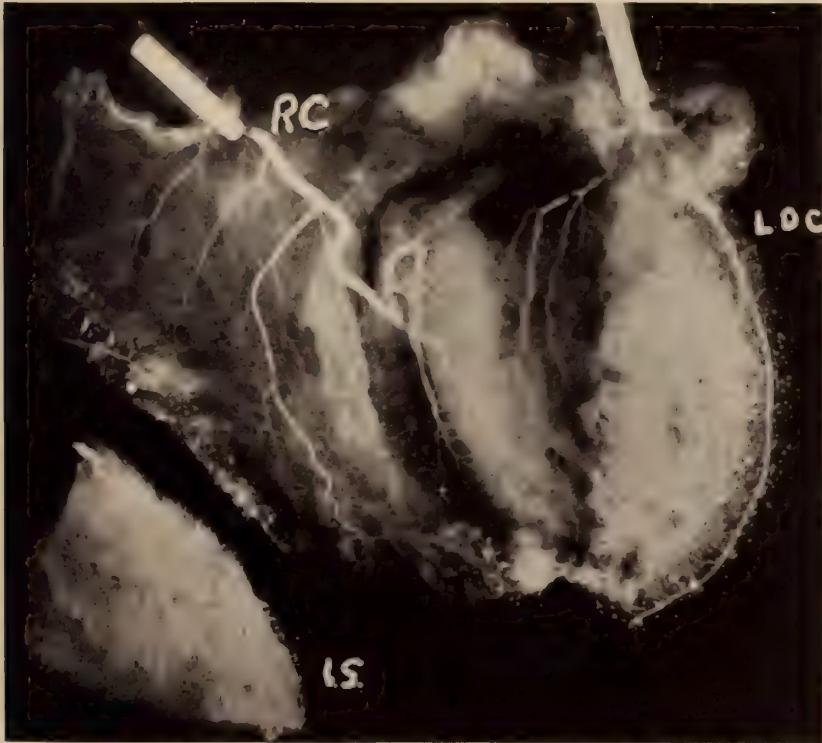


FIG. 2. 27 year old male died of uremia following pyelonephritis. Only left coronary artery injected.

IS, interventricular septum.

RC, right coronary artery.

LDC, descending branch of left coronary.

with resultant mixture of color made it impossible to decide definitely about collateral circulation by this method. So many overlapping vessels existed at the junctional zone that it was impossible to decide if there were direct communications. For this reason, we have been injecting only *one* coronary artery and then taking the x-ray (fig. 2 and fig. 3). If the material is found on the opposite side, it must mean collateral circulation is present. If coronary disease was found in the x-ray and in the subsequent dissection, such hearts were not included in this series.



FIG. 3. 21 year old female died of toxic cirrhosis of the liver. Only right coronary artery injected.



FIG. 4. 3 year old male died of tuberculous meningitis. Only right coronary artery injected.



Fig. 5. 23 year old female died of brain tumor. Only anterior descending branch of left coronary artery injected.

When the opaque mixture was injected into either the right or left coronary artery, the entire arterial system was filled. This is also true of the infant's heart which was injected from one artery only (fig. 4). Even in the only heart in which no collateral circulation was revealed by the perfusion study, we were able to demonstrate that a communication must be present. Injection of the right coronary artery resulted in a filling of the entire coronary arterial tree.

We have found that all the vessels can be filled in normal hearts, if the opaque mass is injected into only the anterior descending or the circumflex branch of the left coronary artery (fig. 5). This indicates that collateral circulation exists to that important vessel which is subject to so much occlusive disease, both acute and chronic. The volume of the collateral circulation to the branches of the main coronary arteries is now being determined by a modified perfusion method.

It was considered theoretically possible that the radiopaque mass might consist of particles smaller than red blood cells and pass through channels which are too small to accommodate red blood cells and, therefore, have no clinical significance. For this reason, in one preliminary experiment, 100 cc. of whole oxalated blood with a red blood count of 3,300,000 per cu. mm. and hemoglobin 61%, were injected into the left coronary artery of an infant's heart age 6 weeks. In a few minutes the blood appeared in the cannula tied into the mouth of the right coronary artery. Determinations of the red blood count and hemoglobin of the blood collected from the cannula in the right coronary were essentially the same, the red blood count being 2,980,000 per cu. mm. and the hemoglobin 63%. From these preliminary observations which are now being repeated and amplified, it is concluded that the diameters of the collateral vessels are large enough to accommodate red blood cells. In the future we plan to determine the exact size of collateral vessels by injecting particles of varying diameters, and also determine the size of the collateral vessels in diseased hearts.

DISCUSSION

In this report, we have presented only the results of our findings in normal hearts. The important problem of the volume of the collateral coronary circulation of diseased hearts will be considered in a subsequent publication.

The important question that is raised immediately is how beneficial to the heart is collateral circulation in the range indicated by these observations. Is the amount sufficient to prevent infarction? Investigators in the past have usually stated that collateral circulation was or was not important without knowing its exact volume. We feel that the importance of collateral circulation depends upon its magnitude plus other circumstances to be described below. This problem will be discussed more thoroughly in a later paper now in preparation on arteriosclerotic hearts.

Here, however, they may be briefly referred to by simply stating that it would seem to us that the effectiveness of the collateral circulation depends upon two factors other than the magnitude of the collateral circulation: the size of the occluded vessels and the metabolic needs of the ischemic muscle.

If the occluded vessel is large, collateral circulation would help preserve the periphery of the infarcted area, but the central zone would necessarily undergo necrosis. If the ischemic area is very small, any collateral circulation may be sufficient to maintain completely the metabolic needs of that area so that no functional insufficiency or structural change of that area results. If the ischemic area is intermediate in size, varying degrees of myocardial insufficiency without necrosis might take place because the blood supply is sufficient to maintain the anatomical integrity of the muscle, but insufficient to perform its normal function.

Finally, the metabolic needs of the muscle must be considered. If the work of the heart is very small at the time of and following the occlusion, the metabolic needs of the infarcted area will be relatively small so that a relatively small amount of collateral circulation may be sufficient to maintain the anatomic and functional integrity of the heart. If, on the other hand, the metabolic demands of the muscle are increased as a result of increased work, which may result from lack of proper rest, valvular disease, increased metabolism from hormonal stimulation, etc., functional changes with or without striking myocardial changes are more likely to occur.

There is another point that needs emphasis. The collateral vessels in a normal heart are already present and are ready to function *immediately* if the blood supply to any area is decreased.

CONCLUSIONS

1. A quantitative method for determining the percentage of collateral circulation between the right and left coronary arteries is presented.

2. This procedure was performed on 12 normal hearts from patients ranging in age from three to sixty-seven years. Collateral circulation was found in all but one; the range being from 0 to 8.6 per cent. The average value obtained was 4.16 per cent. The average flow from the left to right coronary artery was 19.2 cc. or 4.55% of the flow through the left coronary artery, while the average collateral flow from the right to the left coronary artery was 6.2 cc. or 4.05% of the flow through the right coronary artery.

3. The collateral circulation which has been demonstrated between normal coronary arteries, is ready to function immediately when the need arises.

4. If a radiopaque substance, having a viscosity approximately that of blood, is injected into either coronary artery of a normal heart, the entire

coronary artery bed is filled, further proving the presence of collateral circulation.

5. If this same radiopaque substance is injected into the anterior descending or the circumflex branch of the left coronary artery of normal hearts, the entire coronary artery tree is filled.

6. It has been shown that collateral vessels are sufficiently wide to permit passage of erythrocytes. This proves the physiological usefulness of the collateral vessels.

7. The efficacy of the collateral circulation between the coronary arteries and its branches probably depends not only on the magnitude of the collateral, but also on such other factors as the size of the occluded vessel and the metabolic needs of the ischemic muscle.

We desire to thank Miss Janet Wharton for her technical assistance.

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DISPLACEMENT OF THE RS-T SEGMENT BY POTASSIUM CHLORIDE¹

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INTRODUCTION

Wiggers (1) in 1930 applied potassium salts to the epicardium and noted a high S-T take off. Since that time, Herzog (2) 1934, Pescador and Alvarez (3) 1935, Pezzi *et al* (4) 1937, Colombi (5) 1938, Boyd and Scherf (6) 1934, and Nahum, Hoff and Kisch (7) 1941, have repeatedly reported the S-T displacements. Wiggers interpreted the displacement as evidence that chemicals were absorbed from the pericardium and that chemicals which injure conduction produce the same electrocardiographic changes as those produced by interference with the coronary blood supply. Herzog as well as Pescador and Alvarez believed that some reflex action produced the shift. Pezzi obtained S-T displacement only when the left apex was injured and, finding the changes absent in the presence of theophylline with ethylenediamine and after coronary ligation, thought a reflex was initiated at the apex resulting in coronary spasm. Colombi was unable to confirm a circulatory disturbance. He also regarded the apex as the only point where mild mechanical or chemical trauma caused S-T shifts. Boyd and Scherf studied the effect of mechanical irritation (sandpaper, light blows, pinching) and of application of concentrated salt solution. They found "a high take off in Leads II or III regardless of whether an area on the surface of the left ventricle or the apex of the right were irritated." At the right apex S-T₁ was depressed, at the left apex the S-T₁ was not regularly shifted in one direction and no electrocardiographic alterations were obtained from the anterior wall of the right ventricle. They observed that isolation of the irritated area from neighboring tissues (lungs, etc.) diminished or abolished the high S-T take-off and concluded that these shifts were caused by the admixture of a monophasic current of injury in the electrocardiogram.

Nahum, Hoff and Kisch reported similar studies and concluded that surface effects masked deep effects. From other experimental data where the whole surface of one ventricle was painted with M/5 KCl they conclude that the electrocardiogram of one ventricle can be blocked and reaffirm the conclusion of the German school (with which Lewis (8) agreed) that

¹ Acknowledgment is gratefully made to the Hendricks Fund for the support of this work.

the electrocardiogram is a summation of a dextro and a laevo cardiogram. In a later paper, they find that "an elevation of R-T in the cat, dog, or monkey indicates left ventricular injury," and that "S-T depression indicates right ventricular injury," that if the injury is restricted to one ventricle, the RS-T interval in the three conventional leads is deflected in the same direction, that elevation in one lead and depression in another indicates damage to contiguous areas of both ventricles, and finally that an elevated S-T₁ and a depressed S-T₃ indicates an anterior lesion while the reverse relation of S-T₁ and S-T₃ indicates an apical or a posterior lesion.

Ashman and Hull (9) state that "in numerous experiments on turtle ventricles after injury and after application of potassium, the R-T level was never observed to go *below* the isoelectric line, that is, become negative. Of course, when monophasic curves are recorded, the level will remain *above* that line."

One cannot read the above summary without realizing conflicts. First regarding actual observations; some have reported that these RS-T shifts occurred only when chemicals were applied to the antero-lateral surface of the right ventricle. Most workers have reported upward displacements of RS-T_{2, 3} and variable slight shifts of S-T₁, while only one has reported that S-T₃ depression is characteristic of right ventricular injury. One group reports that surface applications are effective while deep injections are not. Interpretations and conclusions must be as variable as the observations upon which they are based. Thus there have been offered absorption, reflexes affecting coronary flow, "perturbation of the myocardial elements which form the whorl at the apex," admixture of a monophasic current of injury, "extinction of activity in one region permitting recording of activity in another region," and surface effects as possible explanations. The necessity for further study seems obvious.

METHODS

Most of our experimental animals were dogs, though a few rabbits and cats have also been used. The anesthetic was 35 mg. per kg. of soluble Pentobarbital, and while maintaining artificial respiration, the thorax was opened, the ribs resected, and the opened pericardium caught to the skin; thus a snug cradle arranged to keep the heart in a constant position. Application of M/5 KCl was made to the heart surface with slightly moistened, one centimeter squares of filter paper. The pericardium was likewise kept free of excess fluid. The main variations from the technique of Nahum, Hoff and Kisch were: 1) the animals were kept on their backs throughout the experiment; 2) chemicals were applied to one muscle band alone, at one time, either for surface application or for deep injection; 3) the three conventional leads were recorded simultaneously on a research instrument built by the Cambridge Instrument Company. When deep injections were made, a dye was added to the M/5 KCl so that the area

could be identified at autopsy. A recovery period was allowed between applications and/or relatively few injections were made in any one heart so that lesions could be identified at autopsy.

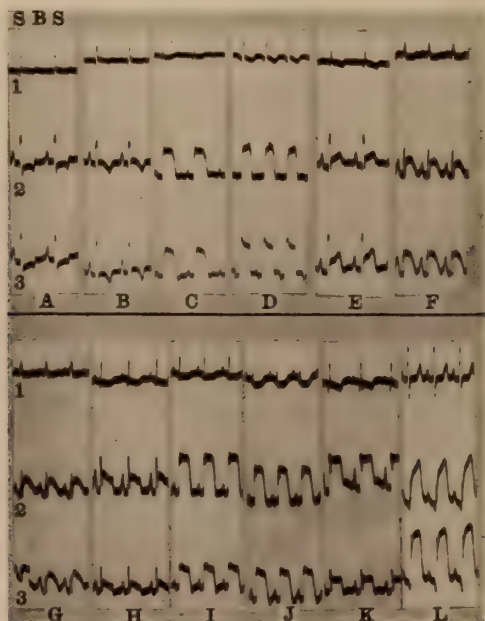


FIG. 1. Electrocardiograms showing effects of 1 cm. sq. pieces of filter paper moistened with M 5 KCl applied to the surface of the superficial bulbospiral muscle (SBS). Doses are indicated whenever deep injections were made. Note throughout that S-T₁ is depressed and S-T₂ elevated.

Time: heavy lines = 0.1 sec.

Standardization: 1 mv = 1 cm.

A. Control: between each application time was allowed for recovery to the normal, but to save space the intervening controls are not reproduced.

B. Left base anterior 1.5 cm. to left of interventricular (I.V.) groove.

C. Obtuse margin, midway base to apex.

D. Near posterior I.V. groove, (0.3 cc. injected) midway base to apex.

E. Left base, diaphragmatic surface 1.5 cm. to left of I.V. groove.

F. Lower third of left diaphragmatic surface near I.V. groove.

G. Lower third of right ventricle, diaphragmatic surface.

H. Left apex, base of inferior papillary muscle (posterior horn).

I. Antero-lateral portion of right ventricle near apex (injected 0.3 cc.).

J. Right apex anterior (injected 0.3 cc.).

K. Left apex posterior (injected 0.3 cc.).

L. Greatest displacement ever obtained, from injection 2 cc. into left inferior papillary.

RESULTS

1) RS-T displacements in one or more of the three standard leads occurred when M/5 KCl was placed anywhere on the ventricular surfaces (figs. 1, 2, 3).

2) In general, the displacements were greater in amplitude at the apices and less at the bases (compare fig. 1, band H). The right ventricular conus was an exception, for there the displacements were marked (fig. 2 B).

3) If a deep injection was limited to one muscle² (and so proven at autopsy) the S-T displacement was as great, or in some instances greater, than when surface application was made (compare fig. 1 G and I, H and K; fig. 2 B with D and E).

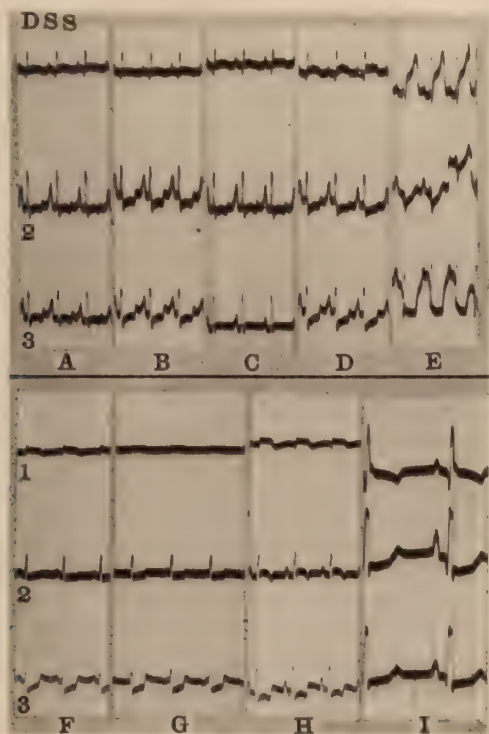


FIG. 2. Application of M 5 KCl to the deep sinospiral muscle (DSS). (Note throughout elevation of S-T₁ and depression of S-T₃)

- A. Control.
- B. Application to conus of right ventricle 1.5 cm. to right of Anterior Interventricular groove.
- C. Control.
- D. Injection of 0.3 cc. M/5 KCl to same area.
- E. Greatest displacement ever obtained, from injection (1 cc.) into conus area of right ventricle.
- F. Left base diaphragmatic aspect (0.3 cc. injected); not near septum.
- G. Right base diaphragmatic aspect (0.3 cc. injected); not near septum.
- H. Left head DSS- near obtuse margin, midway apex to base, half way between endocardium and epicardium. (Injection of 0.5 cc. M/5 KCl)
- I. Lesion in same area caused by coronary ligation resulting in an anemic infarct, demonstrated at autopsy 7 months later.

4) It is true that ST may be elevated in lead I and depressed in lead III (or the reverse), but we do *not* confirm the belief that this occurs only at contiguous left and right ventricular areas nor do we find ST₃ depression limited to right ventricular application. Such records are also obtained

² For description and photographs of the ventricular muscles see: Robb, J. S. and Robb, R. C.: *Am. Heart J.*, 10: 287, 1935 and also *idem*, 1941. In press.

from injections into the deep sinospiral muscle, on the left as well as on the right (anterior, lateral or posterior surfaces), quite independent of proximity to the interventricular grooves (fig. 2 B, F, G, H).

5) It is also our experience that the ST_1 is depressed if M/5 KCl is applied or injected into the right apex, while ST_2 and 3 are greatly elevated

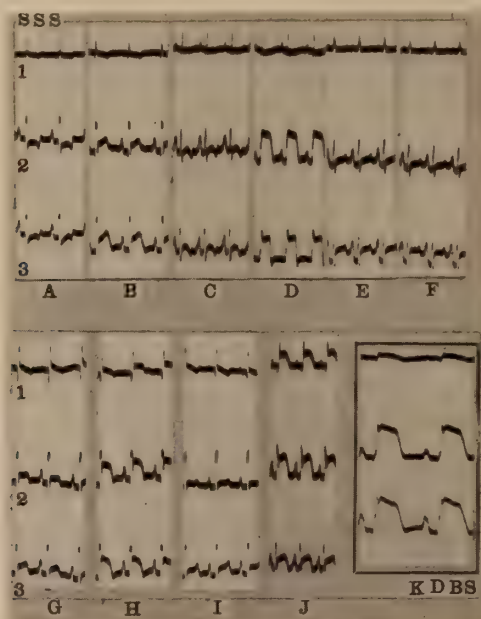


FIG. 3. Application of M/5 KCl to the superficial sinospiral muscle and to the Deep Bulbospiral. Note the upward displacement of RS-T in all leads, moderate in degree in leads 2 and 3, least in lead 1.

- A. Control.
- B. Left base posterior—where this muscle attaches near the septum to the posterior curve of the left a-v ring.
- C. Right acute margin midway between base and apex.
- D. Right antero-lateral border midway between base and apex (some SBS effect since this is the borderline area between the two superficial muscles).
- E. Trabeculated area right ventricle anterior.
- F. On border of SSS and SBS at the anterior I.V. groove, hence $S-T_1$ is isoelectric.
- G. Nearer base on surface left ventricle anteriorly.
- H. On obtuse margin of left ventricle midway between apex and base.
- I. Anterior surface of left ventricle, anterior horn of apex.
- J. Same area but 0.3 cc. injected into anterior papillary muscle.
- K. Injection 1 cc. into septal portion of deep bulbospiral. Note that the R-T elevation is maximal, there being scarcely any downstroke of R in any lead.

(fig. 1 G). This observation does not confirm the opinion that "R-T elevation indicates left ventricular damage."

6) When M/5 KCl was applied anywhere along the course of the superficial sinospiral muscle, the S-T interval in all leads was slightly elevated (fig. 3 B to J).

7) When M/5 KCl was applied along the course of the superficial bulbospiral muscle, whether right or left, apical or basal, anterior or posterior,

S-T₁ was slightly depressed and S-T₃ elevated (fig. 1 B to L). These displacements for areas of similar size are greater near the apex than near the base. The only variation was found at the left base anteriorly where S-T₁ was sometimes isoelectric or even slightly elevated (possibly a deep sinospiral muscle effect appearing through fenestrations in the superficial bulbospiral).

8) Where the deep sinospiral muscle appears on the surface through fenestrations (right and left bases, either anterior or posterior) or when M 5 KCl is injected into any part of this muscle, S-T₁ is elevated and S-T₃ is depressed (fig. 2, B to I).

9) When M 5 KCl is injected into the deep bulbospiral muscle (which never reaches the surface but encircles the base of the left ventricle) a maximum elevation of RS-T is obtained in all leads, again not confirming the supposition that surface effects are necessarily greater than the results of deeper injuries (fig. 3 K). It may be emphasized that this was a septal lesion, nevertheless, the displacements are all upward and no Q wave is present.

10) These RS-T shifts are exactly those which have been previously described when these same muscles were damaged either by ligating the individual blood supply or by undue stretching associated with increased intraventricular pressures (Compare fig. 2 H and I).

11) These observations do not support a conclusion that the electrocardiogram is a summation of only two events, a dextro and a laevo cardiogram.

DISCUSSION

It is commonly believed that potassium chloride when applied to conducting tissue, e.g., nerve, abolishes the propagated disturbance (action current) and also abolishes the injury current. Nahum, Hoff and Kisch (7) believe that it "extinguishes electrical activity". Ashman and Hull (9) state more specifically that "potassium in sufficient concentration, produces a depolarization of cell membranes. With lesser concentrations, the depolarization is partial". Their discussion of the monophasic action current and the current of injury is pertinent to this discussion. Their figure 6 illustrates various types of monophasic action current recording. We especially wish to stress the concluding sentences of that section "*We may note that injury is not necessary for the production of a monophasic response. The only essential condition is the presence of properly oriented cell membranes, which fail to respond to a wave of excitation and which form the surfaces of portions only of whole cells*".

We suggest that the division of the ventricle into muscle bands separated from each other by variable amounts of connective tissue, each muscle having to a considerable extent its own blood supply (Robb, Lowe) supplies this very essential condition of which Ashman and Hull write.

We also suggest that the production of maximal displacements near the

apex is related to the anatomical fact that the two superficial muscles are there condensed into narrow intertwining bands so that these membrane effects might be more pronounced. Also at the apex application of potassium to a small area might affect many conduction pathways which are there condensed, whereas toward the base the muscles spread out fanwise in thin sheets. Application of potassium to 1 sq. cm. at the base causes far less effect than at its apex but by increasing the area covered, the RS-T displacement can be made to equal that at the apex.

CONCLUSIONS

1. Application of potassium chloride to the surface of the mammalian ventricle does not necessarily cause a greater RS-T displacement than does deep injection.

2. No support is obtained for the theory that the electrocardiogram is merely the summation of a dextro- and a laevo- cardiogram.

3. When leads I and III show RS-T deviation in opposite directions the lesion is not necessarily near the septum nor is the lesion necessarily anterior or posterior. When all three standard leads show an RS-T deviation in one direction the lesion is not necessarily limited to one ventricle.

4. It is again shown that where "injury" is limited to a single ventricular muscle band, a characteristic electrocardiogram results. "Injury" may be of various types, chilling, mechanical blows, pinching, ischemia, undue stretching, or the application of potassium chloride, in fact any agent resulting in the depolarization of a membrane. We have shown that regardless of the type of noxious agent, the result of injury localized to one muscle alone is constant in its effect on RS-T shifts in the electrocardiogram.

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INSULIN HYPOGLYCEMIA AND VASCULAR ACCIDENTS IN DIABETES MELLITUS

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My admiration and appreciation of Dr. Oppenheimer and his methods date back to my first acquaintance with him when he was assigned to Camp Devens in 1918. It has been a satisfaction to see his influence widen. Unfortunately, I could not contribute an article for his Anniversary, but my associates, Dr. Howard F. Root and Dr. Charles Styron, submit in my behalf their paper on "Insulin Hypoglycemia and Vascular Accidents."

ELLIOTT P. JOSLIN

INTRODUCTION

The protean manifestations of hypoglycemia have simulated every known neurologic and psychic abnormality. The difficulty of diagnosis between hypoglycemia and vascular accidents may be great when one condition alone is present, but is increased in the presence of both. The danger of errors in diagnosis naturally rests upon the fact that insulin hypoglycemia is an emergency state for which there is specific treatment. Delay in administering the treatment may have progressively serious results. In an occasional case important medico-legal problems arise, illustrated by serious automobile accidents involving passengers or pedestrians.

The hazard of injurious effects upon the heart in cases with coronary disease provoked by the use of insulin in diabetic patients has been discussed frequently. The hypothesis has rested apparently upon an occasional anginal attack after the administration of insulin to cardiac patients. Actually the experimental production of coronary occlusion in animals by means of insulin has not been reported. Indeed, there has been no evidence of damage to the heart in fatal cases of insulin hypoglycemia. It is generally conceded, however, that following insulin hypoglycemia changes occur varying in degree with the individual, the amount of insulin injected and the state of the counter-regulatory system. In the presence of hypoglycemia there is an output of adrenalin with a concomitant rise in the pulse rate and metabolism and thus indirectly cardiac strain is caused.

Hypoglycemia is relieved by the liberation of glucose from the glycogen in the liver. The lack of evidence of damage in the heart following hypoglycemia dovetails at present with the lack of evidence that the heart muscle is dependent exclusively upon carbohydrate. On the other hand, the chance exists that patients with serious coronary disease can have harmful effects produced by the events following a serious insulin hypoglycemia. Further comment on cardiovascular disease follows the case reports. Where the question of cerebral damage and vascular accidents in the brain is raised, the problem is a somewhat more difficult one.

Whereas parenchymatous cerebral damage has been described in detail, the actual damage to the vessels with resulting focal changes is a different problem and as yet little known.

Insulin hypoglycemia is of common occurrence and usually harmless if prompt treatment is given. Transient monoplegias or even hemiplegias are not rarely encountered in patients, especially children, and yield promptly to the administration of carbohydrate.

CASE REPORTS

I. Insulin hypoglycemia simulating a cerebrovascular accident

Case #10772. The patient developed diabetes at the age of forty-one years in June, 1927. His maximum weight in 1916 was 194 pounds dressed. On February 13, 1932 he weighed 130 pounds. During that year he had had several attacks of mild angina pectoris. Beginning with December 1932, he took 16 units of insulin once a day. He had occasional attacks of mild angina pectoris on exertion, particularly in cold weather. On September 13, 1937, at 1:00 p.m. he was brought to the Deaconess Hospital in an unconscious state. His daughter stated that he had been apparently well the night before. He had taken a moderately long walk during the day and had retired at 10:00 p.m. During the night he was heard to groan, but he was not obviously disturbed. The following morning at about 10:00 a.m. he failed to rise for breakfast and could not be awakened. A doctor was called, who administered 1 cc. of adrenalin and 45 units of insulin. On the way to the hospital, he was given one ampule of 25 per cent glucose solution intravenously. Upon arrival his face was flushed, his skin was warm, and the extremities were dry. The arms were held in a flexed position and were rather spastic; the legs were extended. Later he presented a picture of decerebrate rigidity arousing the suspicion of a pontine lesion. The blood pressure was 130 systolic and 80 diastolic; the pulse rate was 116 per minute; the heart, lungs, and abdomen were negative. The first blood sugar value was 80 mg. per cent. One hour later the blood sugar was 70 mg. per cent. He was given 1000 cc. of normal saline solution with 10 per cent glucose at 2:00 p.m. and the blood sugar was 200 mg. per cent at 3:30 p.m.

At 7:00 p.m. the blood sugar was found to be 26 mg. per cent. He was then given an injection of glucose solution and from that time on the blood sugar values were kept between 200 and 290 mg. per cent.

The cerebrospinal fluid was normal.

He remained in a comatose state for a period of three weeks and finally died with terminal bronchopneumonia and sepsis.

Post-mortem examination by Dr. Shields Warren showed a recent splenic infarct, bilateral bronchopneumonia with gangrene and abscess formation, abscesses of the kidney, cystitis, and pyelonephritis.

Brain. Gross anatomy (Wt. 1550 gms.). There was slight widening of the sulci in both frontal areas. The hemispheres were symmetrical and the convolutions narrow. The arachnoid was clear and glistening with the exception of the frontal lobes where there was cortical atrophy with thickened arachnoid. Coronal sections 1 cm. thick showed the cortex to be approximately 4 mm. thick. The white matter was not unusual. The lateral ventricles were normal in size and symmetrical. There was dilatation of the left posterior horn measuring 2.5×3 cm. The adjacent brain tissue was normal. The third ventricle at the level of the mammillary bodies was 0.8 cm. wide and 1.8 cm. high. The cerebellar hemispheres were symmetrical. There was a moderate foramen magnum pressure furrow. There was moderate sclerosis of the basilar arteries with a few plaques of calcium. This was also true of the circle of Willis. Sections of the medulla and the pons were negative except for moderate edema of the tissue adjacent to the fourth ventricle.

Microscopic: Sections showed slight edema near the cerebellar peduncle and portion of the pons.

Heart. Gross anatomy (Wt. 260 gms.). The epicardium was smooth and glistening with a moderate presence of fat. There was a diffuse, grayish area about 2 cm. in diameter over the right side of the left ventricle, midway between the base and the apex. The myocardium was generally firm, reddish-brown, but showed defects in two areas. The right side of the apex of the left ventricle was thin, firm, and white over an area 1.5 cm. in diameter. Two centimeters below the mitral valve in the myocardium of the left ventricle near the interventricular septum was an area 1 cm. in diameter where the myocardium was firm, pale-brown, and 0.7 cm. thick with the adjacent myocardium 1.4 cm. thick. The endocardium over this area was pale, opaque, but elsewhere smooth and glistening. The valves were normal. The coronary arteries showed slight intimal thickening.

Microscopic: There were small irregular areas of fibrous tissue extending in one area from the endocardium to the epicardium.

Summary. In this case presumable insulin hypoglycemia was followed by unconsciousness which persisted until death 23 days later. No focal lesions in the brain were found and the heart showed the remains of an old infarct. Death was due to terminal pneumonia and sepsis.

II. Insulin hypoglycemia and simultaneous cerebral thrombosis

Case #2681. This patient developed diabetes in April 1922 at the age of 44 years. His maximum weight was 196 pounds dressed. The blood pressure was 130 systolic and 80 diastolic. The heart, lungs, and abdomen were normal. The dorsalis pedis arteries were palpable and patent. In 1923 he began taking insulin, a total of 35 units a day. In 1928 the insulin dose was decreased to 29 units daily and his weight was 153 pounds dressed. From that time on he was seen only at rare intervals. His blood sugar was kept within normal limits and as a physician he tended to overtreat himself. Thus, he occasionally had insulin reactions between 11:00 and 12:00 a.m. He never had a severe reaction, however, except on one occasion when a convulsion occurred while he was eating supper. In 1933 the blood pressure was 150 systolic and 100 diastolic. The heart, lungs, and abdomen were in satisfactory condition. On September 20, 1936 he returned home at 9:00 p.m. after being away for a week-end. He seemed a little confused and tired. Supper had been omitted and at 11:00 p.m. he took a dose of insulin while already in a confused state of mind probably due to hypoglycemia. His wife was awakened at 3:00 a.m. by his noisy cries. She found him on the floor in a pool of blood from a laceration of the nose. His feet shook but there was no real convulsion. His right leg and arm were flaccid. The urine was sugar free. Carbohydrate as orange juice was given freely during the next few hours. He did not regain consciousness and did not speak during the succeeding 12 hours.

On entrance to the Deaconess Hospital the urine contained 7.7 per cent sugar and the blood sugar was 0.22 mg. per cent. As a result of the large amount of carbohydrate given prior to entry the urine showed a good deal of sugar during the ensuing week despite repeated small doses of insulin. In consultation with Dr. G. C. Caner it was found that in addition to a right hemiplegia there was a positive Chaddock and Babinski response on the left. His pupils were first dilated and later constricted. Respirations were of the Cheyne-Stokes type. His fundi were normal. He died on September 29, 1936 without regaining consciousness. From the complete autopsy report of Dr. Shields Warren we give only the description of the brain and heart.

Brain. Gross anatomy (Wt. 1400 gms.). The left hemisphere was slightly larger than the right and an area supplied by the middle cerebral artery, which involved the major portion of the parietal lobe, the adjacent two-thirds of the frontal lobe and the superior gyrus of the temporal lobe, was soft and bulging. The meninges over this area were hyperemic and somewhat opaque. The gyri were flattened and the sulci were extremely shallow. There was a definite pressure cone at the base of the brain. The vessels at the base of the brain showed considerable sclerosis. Coronal section showed severe softening in portions of the left parietal, frontal, and temporal lobes. The left ventricle was small and the ependyma of the left ventricle over the involved area was dull. The left middle cerebral artery near its origin was occluded by an organizing clot.

Microscopic: A section of the left lenticulo-striate body showed areas of demyelination, recently thrombosed vessels, small hemorrhages, and areas of inflammatory cell infiltration, chiefly leucocytes. A section of the left thalamus showed less severe change. Many ganglion cells were rounded and showed indistinct nuclei. Sections of the pons and cerebellum showed no unusual change except for rounding of ganglion cells and nuclear disappearance. Section of the left precentral cortex showed areas of softening with many compound granular cells. The meningeal vessels were dilated and hyperemic. The surrounding stroma showed proliferation and many histiocytes containing debris.

Heart. Gross anatomy (Wt. 350 gms.). The epicardium was thin, smooth and glistening. The myocardium was of average thickness throughout, quite firm and brownish-red. There was no grossly visible fibrosis or fat infiltration. The endocardium was thick and transparent throughout. The auricular appendages appeared normal. The valves, of average circumference, were normally developed and showed no thickening, fusion, nor widening of commissures. There was a small amount of yellow, pliable sclerosis in the septal leaflet of the mitral valve. The papillary muscles and columnae were robust and not flattened. The chordae tendineae were thick and delicate. The coronary ostia was ample. There was a mild intimal sclerosis of the proximal 2 cm. of the left coronary artery, but otherwise no appreciable sclerosis of the coronaries. There were no areas of appreciable lumen reduction.

Microscopic. Sections showed no unusual change. The arteries of the heart showed no thickening.

Summary. No blood sugar was taken prior to hospital entry. However, the clinical history supports the assumption that an insulin reaction occurred. Whether or not the hypoglycemia preceded, accompanied, or followed the cerebral thrombosis and infarction is not clear.

III. Insulin hypoglycemia or cerebral hemorrhage

Case #20520. The patient developed diabetes September 1931 at the age of 45 years. His maximum weight in 1931 was 230 pounds. He weighed 184 pounds on September 7, 1941. In January 1941 while working in a bleachery as foreman he barely escaped being burned in a vat of a caustic solution and was greatly frightened.

Thirty minutes later, while driving his automobile he suddenly lost the use of his right arm and had difficulty with speech. A doctor made a diagnosis of insulin reaction and gave him glucose, with prompt recovery in the use of his arm and speech. Since that time the use of the arm and speech seemed normal under ordinary circumstances, but under stress and strain both were somewhat affected. His blood pressure was 140 systolic and 80 diastolic. The heart was not enlarged. The lungs and abdomen were essentially normal. His diabetes was of moderate severity. The urine contained 2.8 per cent sugar on admission. He was treated with 10 units of crystalline plus 20 units of protamine zinc insulin and with this dose the urine sugar was reduced to 0.3 per cent in the twenty-four hour amount and the blood sugar values on the last hospital day were 0.14 per cent fasting and 0.15 per cent at 4:00 o'clock. His blood pressure varied. On one occasion it was 180 systolic and 110 diastolic when sitting erect, 160 systolic and 90 diastolic after lying down for a few minutes talking quietly. When, however, he described his narrow escape the pressure rose to 170 systolic and 108 diastolic.

Summary. Insulin hypoglycemia may have been present when cerebral hemorrhage or thrombosis occurred. The subsequent events suggest that a vasospastic crisis accompanied an insulin reaction which was associated with, or caused a small area of thrombosis or hemorrhage.

Frequency of insulin hypoglycemia in the hospital. During the first four months of the year 1941 one of us (CWS) studied all insulin reactions among the patients of the George F. Baker service at the New England Deaconess Hospital. The blood sugar values, the urine tests, and above all the symptoms and other clinical features of the condition were recorded. In these four months 75 patients among a total of 600 diabetic patients (1 in 8) were treated for 205 attacks of insulin hypoglycemia. Included in the group were three patients who were in the hospital for periods of three to four months for special insulin investigation. These three patients had a total of 55 insulin reactions and, because of the special character of their hospital treatment, should be excluded from this series. We may, therefore, say that the 150 reactions were limited to 72 patients. This fact alone indicates that any patient who is undergoing rapid hospital treatment and who has one insulin reaction is apt to have a second or even a third reaction. These 72 patients under treatment ranged from 4 to 76 years of age. The duration of their diabetes ranged from a few weeks to 19 years and their insulin treatment from a few days to 18 years. Only one patient had taken insulin for 18 years. The group in fact represented a total of about 532 years of diabetes mellitus and 480 years of treatment with insulin. Three patients were between 4 and 9 years of age, 39 patients from 10 to 29 years of age, 14 patients from 30 to 45 years of age, and 11 patients from 45 to 59 years with 7 patients in the period from 60 to 76 years of age. A wide variety of vascular disease was found in the group. Twenty-five patients or more than one-third of the group had hypertension as shown by blood pressure values in excess of 140 systolic and 90 diastolic.

In the 205 insulin reactions, not one resulted in a vascular accident of any sort and this in spite of the fact that in a few cases there were gen-

eralized convulsions and in one, Jacksonian seizures. In no instance was anginal pain present during the attack and in only five instances was subjective palpitation of the heart described. One patient was in severe congestive failure on admission and during hypoglycemia some dyspnea was noted.

Few insulin reactions are observed in elderly patients with hypertension or cardiovascular disease. However, it must be remembered that such patients do not have the wide variation in physical activity which is so characteristic of young patients. It is well known that muscular exercise increases the activity of insulin and explains many of the insulin reactions so common in young people. Also, this elderly group of patients have lower rates of metabolism and therefore usually require smaller amounts of insulin. Nevertheless, it is still true that hypoglycemic reactions can occur in the presence of occlusive vascular disease even with small doses of insulin.

Case #17518. A man 77 years of age developed diabetes in January 1937. At this time, the urine contained 4.6 per cent sugar and the blood sugar was 0.40 per cent. His arteries were thickened and typically beaded. Pulsation could hardly be felt in the dorsalis pedis arteries. His blood pressure was 180 systolic and 100 diastolic. He became sugar free with a small dose of insulin. On February 11, 1939 he had taken his usual 6 units of insulin in the morning before breakfast. Following a heavy snowfall about 4:00 o'clock in the afternoon, he did a great deal of unusual work in shovelling snow off a long path. The next morning he was delirious from a low blood sugar. Immediate relief occurred with the taking of orange juice. Only a few months later he lost one leg from diabetic gangrene.

It is a fair inference that the above rate of insulin reactions is maintained throughout the year at the New England Deaconess Hospital. Therefore, in 1500 to 1800 patients in a year, we have 600 to 700 insulin reactions which are recognized by the patient or nurse. One might ask if such a series is overloaded with patients who come to the hospital because of the occurrence of insulin reactions outside. It is true that in the series of 72 patients 5 patients, but only 5, came to the hospital for adjustment because of insulin reactions outside the hospital. Errors in the diagnosis of hypoglycemia may arise and are only avoidable by observing the rule that the blood sugar is to be determined in any patient who thinks he is having a reaction.

The possibility of error in diagnosing an insulin reaction is illustrated by a patient who entered the hospital because she thought she was having insulin reactions on 2 units of insulin a day. Actually, we found that her diabetes was quite uncontrolled. She was having frequent attacks of angina pectoris. When the diabetes was brought under control by increasing the insulin dose to 20 units of protamine zinc insulin, the attacks practically disappeared. It is true that she did have on one occasion a mild insulin reaction with a blood sugar of 30 mg. per cent, but at this time she had no cardiac pain.

Certain chemical features stand out in this group of 205 reactions. No true insulin reactions were observed in patients with a blood sugar above 80 mg. per cent. The lowest blood sugar value during an insulin reaction was 15 mg. per cent. This occurred in a woman of 28 years who was taking 16 units of crystalline insulin and 40 units of protamine zinc insulin and who had hypertension, retinitis and albuminuria. She died within a few months of cardio-renal failure. The lowest dose of insulin which resulted in an insulin reaction was 16 units of protamine zinc insulin taken before breakfast and the highest dose of any patient who had an insulin reaction was 44 units of crystalline and 80 units of protamine zinc insulin.

In this series, no patients were unconscious for more than a few minutes after the condition was discovered except one patient who was unconscious with unilateral convulsions from three to five minutes. However, recovery was prompt with glucose solution administered intravenously and no residual symptoms followed.

The reactions occurred chiefly before breakfast and at 11:00 o'clock in the morning. Most of these patients were taking protamine zinc insulin and a smaller dose of crystalline insulin before breakfast. The common symptoms were sweating, weakness, trembling, nervousness, hunger and, in the case of reactions occurring early in the morning before breakfast, due to protamine zinc insulin, occasionally there was headache or nausea. The more severe symptoms which occurred were as follows: 1) mental abnormalities such as delirium, delusion, anger, crying and extreme excitement in 18 cases; 2) drowsiness from which the patient could be aroused by a strong stimulus in 8 cases; 3) unconsciousness in 12 cases; 4) convulsions in 3 cases.

Undoubtedly, the frequency of insulin reactions in the hospital is greater than in patients outside the hospital, in spite of the fact that variations in exercise outside the hospital make it difficult for patients to adjust diet and insulin. Furthermore, most of the instances of a severe insulin reaction occurring outside the hospital do find their way into hospital wards. The occurrence of severe hypoglycemic reaction with symptoms which might easily be confused with cerebral accidents is rare, but of the utmost importance when the problem arises.

Cerebrovascular accidents in diabetic patients. In marked contrast to the incidence of coronary thrombosis and of occlusive vascular disease in the legs leading to gangrene, cerebrovascular accidents in diabetic patients seem no more frequent than in non-diabetic patients. In a report of 70 such cases among diabetic patients at the Deaconess Hospital, Jordan and Waters (1) concluded from the analysis that 7 per cent of all diabetic deaths at that time were due to this cause and there was no reason to believe that its frequency varied from that in non-diabetic patients. They compared this figure with 8.4 per cent for such lesions in 2,400 autopsies at the Cleveland City Hospital reported by Webster in 1929 (2). Wilder (3) also

agrees with these conclusions in writing of his experiences at the Mayo Clinic. The pathologic alterations underlying the cerebral accidents described by Jordan and Waters were dependent upon hypertension and arteriosclerosis. In most diabetic clinics the experience seemed to suggest that the prognosis of diabetic patients was better than what might have been anticipated and, indeed, it was even suggested that diabetic patients seemed to withstand cerebral accidents even better than non-diabetics. It must be pointed out, however, that although 7 per cent for cerebral accidents as a cause of death among diabetic patients was quoted by Jordan and Waters from Joslin's experience, this figure has changed during the last ten years. In a tabulation of 5,659 diabetic deaths from cerebral accidents in the period between 1930 and 1936 the figure had risen to 9.5 per cent and in the period from 1937 to 1940 the figure was 11 per cent of 929 deaths (4). It must be stated that the average age at death has risen from 44.5 years in the period from 1897 to 1914 to 64.8 years for the 927 fatal cases in the period from 1937 to 1940. This increase in the frequency of cerebrovascular accidents must be recognized as a fact dependent largely upon the increasing span of life of the diabetic patient.

Pathology of insulin hypoglycemia. The pathologic changes induced by insulin hypoglycemia in the normal experimental animal or normal human being should be sharply distinguished from the changes which one might presume to occur in the patient with vascular or cardiac disease. In the second edition of Warren's textbook (5) on the pathology of diabetes the effect of both crystalline and protamine zinc insulin is summarized. He states that little is known about demonstrable anatomical changes resulting from insulin hypoglycemia. In both patient and experimental animal, the chief findings have been the changes due to toxic effects upon nerve cells and edema of the brain. Wide use of insulin hypoglycemia in the treatment of mental disease, notably schizophrenia, has given rise to a voluminous literature. The proceedings of the eighty-ninth meeting of the Swiss Psychiatric Association were published in a supplement of a May 1938 number of the American Journal of Psychiatry. Sixty-eight communications dealt with the treatment of schizophrenia with insulin and cardiazol. Since that time many other articles have appeared and references to a number of them will be found in chapters on hypoglycemia and the nervous system by Joslin, Root, White and Marble (6).

Sahs and Alexander (8) describe a man, age 58 years, who was under treatment for an infection of the foot. He was receiving a total of 120 units of insulin a day and on the night of the sixth day he had an insulin reaction with prompt recovery when orange juice was given. On the next day another insulin reaction occurred but then there was no response to the orange juice. One and one-half hours later 40 units of insulin were given together with 1000 cc. of 5 per cent glucose, but the patient did not immediately regain consciousness. Another injection of dextrose was given with the

result that he responded normally. However, once more he lapsed into an unconscious state in which perspiration was produced. This time the blood sugar was found to be zero. No convulsions occurred. Injections of dextrose were given repeatedly, but unfortunately he received 100 units of insulin during the same morning and he died after having been in hypoglycemia for 28 hours.

Careful histologic studies of the brain were made using modern stains. Vessels at the base of the brain showed no gross evidence of arteriosclerosis, but there were moderate atheromatous changes in the coronary arteries. Of special interest was the marked degree of vascular disturbance, including dilatation of vessels with irregularities of caliber and small perivascular hemorrhages. The changes were not specific, since similar changes are observed in cases of carbon monoxide poisoning, in electrical injury, and in occlusion of the large arteries of sixth and seventh orders. Their summary of the pathologic changes are as follows: "irregular dilatation of intracerebral vessels, indicating varying degrees of sluggish flow; multiple thrombi and perivascular extravasations, notably in the basal ganglia and medulla oblongata, but involving other areas as well; foci of blanching in the central and upper parietal regions of the cortex, and interstitial edema with swelling of oligodendroglia cells in the cerebral white matter. . . . Evidence is present to support the anoxic theory of hypoglycemic shock."

It is notable that this is the first case in which small thrombi in very small arterial vessels have been shown in typical cases with insulin hypoglycemia. Actually, in their review of some 27 articles dealing with this subject, the striking feature was the absence of vascular lesions (thrombosis or hemorrhage) caused by the hypoglycemia. Edema and hyperemia of the brain with small cerebral hemorrhages are found in patients who have had severe convulsions and the changes in the nerve cells themselves have been conspicuous.

This case gives evidence of focal pathologic changes which might explain the monoplegia or the hemiplegia occasionally seen at the time of an insulin reaction. On the other hand, it is clear that only small microscopic changes were produced and not areas of hemorrhage or thrombosis of macroscopic size.

The necessity of continuing glucose injections in patients who are unconscious as a result of hypoglycemia, however, is supported by the observations of Pijoan and Gibson (7) who found that within 4 minutes after its injection most of the glucose had been removed from the blood stream.

The effect of hypoglycemia upon patients already suffering with cerebral arteriosclerosis presents a difficult problem because of possible secondary changes produced by hypoglycemia. In addition to the effect of anoxemia, which alone may be sufficiently damaging, there is also the increased blood pressure secondary to adrenalin secretion, increased metabolism, and involuntary activity due to convulsive seizures. Such a combination of

chemical effect and physical activity might well have undesirable results in patients whose arteries are already damaged seriously and whose brain is too vulnerable to stand such insult. It is quite conceivable that thrombosis or fresh hemorrhage might result.

Differential diagnosis. The three cases presented raise a number of questions and a few points for discussion. In the third patient the emotional disturbance produced by fright evidently continued for some time. In the mind of the patient this was the principal factor in producing the condition which he regarded as one of insulin shock. He regarded it as insulin shock because he was so promptly relieved by the intravenous administration of glucose. Unfortunately, his physician did not take a blood sugar before giving glucose. Therefore, we are left with the question as to whether true hypoglycemia was present at all. He did undoubtedly have a paralysis of the right arm and a speech defect which came on suddenly while driving an automobile. This might have had very serious consequences and serious medico-legal reverberations had it chanced that he conveyed passengers at the time. One must not conclude that relief from paralysis is clear proof of the presence of hypoglycemia. The fact that he now has hypertension and that he has some residual weakness of the arm and speech difficulty indicates that a small hemorrhage or thrombosis occurred at the time of the accident.

A patient who has taken insulin for 12 years was feeling well when she jumped from a hayloft into a pile of hay in a game. Immediately she became unconscious in an insulin reaction from which she soon recovered when she was given orange juice.

Dr. Clowes of the Eli Lilly Company states that formerly it was the custom to standardize insulin by giving rabbits one unit of insulin subcutaneously. At the end of four hours the rabbits' blood sugars fell to 40 mg. per cent and a considerable percentage of rabbits had convulsions. The other rabbits, however, remained quiet until some one entered the room and clapped his hands. This sudden auditory stimulus in some way sensitized the cerebral threshold and convulsions occurred. This fact is one of many which may serve to explain the well-known observation that the occurrence of hypoglycemic symptoms with or without convulsions may occur at one level of blood sugar on one occasion and fail to occur with even a lower blood sugar at another time.

In the second case we have a clear picture of extensive vascular disease of the brain and of cerebral thrombosis which may have begun earlier. Of the latter we cannot be certain. The confusion of the patient in the evening when he took a second dose of insulin may have been due to the vascular disease itself rather than to an insulin reaction. Here again there is no clear proof to establish which came first, confusion due to insulin reaction, or mental confusion due to the cerebral vascular disease, but the first seems more likely.

In the first case the exact amount of insulin given is unknown. The fall in the patient's blood sugar to 26 mg. per cent some hours after admission to the Deaconess Hospital indicates an overdose of insulin, either crystalline or protamine insulin. The action of crystalline insulin is very much prolonged when a sufficiently large amount is taken, and the blood sugar had been temporarily maintained by the administration of glucose on his way to the hospital. Clear evidence of vascular disease sufficient to cause degenerative changes in the brain is lacking. We are forced to believe that in this patient irreversible changes in the nerve cells of the brain were produced.

Treatment of insulin hypoglycemia. The urgency of prompt and adequate treatment of insulin hypoglycemia when unconsciousness is present is illustrated by the case of a girl who had been unconscious for five days. The insulin reaction began about 9:30 p.m. and the physician who was called promptly gave 20 gms. of glucose intravenously. Since she did not improve immediately she was sent to the hospital. On arrival one hour later she was again given 25 gms. of glucose intravenously and the blood sugar was taken for analysis. After one hour and a half the blood sugar was found to have risen and no more treatment was given although the patient was still unconscious. Three and one-half hours later the blood sugar was found to have fallen to a low level again whereupon glucose solution was again given. The result was that during the first 16 hours of her hospital stay she had several isolated injections of glucose solution but no continuous intravenous administration of glucose solution. The blood sugar value was, therefore, raised for a brief period but fell again. The explanation seemed to be that she had taken so large a dose of insulin that small amounts of glucose only served to raise the blood sugar for brief periods of time. It makes little difference whether regular insulin or protamine zinc insulin is given. If a large amount of either type of insulin is taken the hypoglycemic effect of the dose may be prolonged for many hours. In ordinary cases of insulin reactions where the symptoms are of short duration, prompt administration of a lump of sugar or 50 to 100 cc. of orange juice will usually be adequate. When a patient has become unconscious it means that already a marked toxic effect has been produced in the brain and an emergency exists. If the condition is not promptly combated, irreversible changes will take place sooner or later. Therefore, where unconsciousness occurs, particularly when insulin has been given to a patient already suffering from hypoglycemia, we find it advisable to give intravenous 10 per cent glucose until the patient is conscious.

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THE MECHANISM OF AURICULAR FLUTTER AND FIBRILLATION

AN HISTORICAL SURVEY

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The evolution of our present understanding of the mechanism and clinical features of auricular flutter and fibrillation is one of the most colorful chapters in internal medicine. It is a conspicuous example of the manifold advantages that accrue to the clinician from the joint endeavors of physiology and experimental medicine. A full appreciation of the clinical manifestations of these disorders became possible only when their mechanism had been indicated by the physiologist and put to test in the laboratories of experimental medicine. Such collaboration had the further fruitful effect of suggesting a rational therapeutic approach.

The term "flutter" was first employed by McWilliam in 1887 (1) to designate a phenomenon resulting from the faradic stimulation of the mammalian auricle in contradistinction to another then well known phenomenon, "arrhythmic fibrillar contraction." That the application of strong constant currents, or faradic currents to the dog's heart caused abolition of the normal beat and threw the ventricles into a state of rapid irregular contraction had been known as far back as 1850 (2). This phenomenon was familiar to McWilliam and others as indicated by the various names, such as Herz-Delirium, Delirium Cordis, Fibrillar Contractions, Intervermiform Movement, which had been employed to designate this disorder.

While studying the phenomenon of fibrillar contraction in the hearts of a large number of mammals, both in the young and in the adult, McWilliam confirmed previous views and added valuable observations of his own. He believed that fibrillar contraction "is essentially due to certain changes occurring within the ventricles themselves" and is not necessarily dependent on the destruction or paralysis of any coordinating center. Among the outstanding features of arrhythmic fibrillar contraction he was especially attracted by 1) the complexity of movement which appeared to be in direct relation to the complexity of arrangement of the muscular fibres; 2) by a rapid heart action, which he believed was the result of "excitation of a highly excitable tissue" and 3) by the persistence of the mechanism. When fibrillation had set in as a result of stimulation "the prolonged continuance of the movement after cessation of the exciting cause," he emphasized, "is a striking feature."

McWilliam made it quite clear that the readiness with which heart muscle is thrown into fibrillary contraction varies remarkably with the different conditions of the cardiac tissues. He pointed out that in the normal vigorous heart, a considerably stronger current is required and that in some instances it may indeed be impossible to produce it at all. Certain changed conditions, on the other hand, such as nutritional disturbances of the myocardium, made it extremely easy to throw the ventricles into fibrillary contraction. It was upon the integrity of the heart muscle that the duration of the phenomenon seemingly depended. In the young mammal, fetal or soon after birth, fibrillar movement was only temporary and recovery appeared to be the rule. The most persistent derangement seemed to have occurred in animals in which the fibrillation was induced by depressing drugs. In these, recovery of normal heart beats was exceptional.

In contradistinction to fibrillary contraction, which McWilliam regarded as a rapid incoordinated peristaltic contraction of the ventricles, the phenomenon resulting from faradic stimulation of the auricles appeared to him to differ in various respects. The application of the current he observed, "sets the auricles into a rapid flutter . . . The movements are regular; they seem to consist of a series of rapid contractions . . . The movement does not show any distinct sign of incoordination; it looks like a rapid series of contraction waves passing over the auricular walls." It was his opinion that the difference between this mechanism and that seen in the ventricles probably depended on the simpler structures and arrangements obtaining in the auricles.

The term "flutter" thus coined by McWilliam, whether his case did represent clear-cut flutter as we know it or an impure flutter or a coarse fibrillation as suspected by Lewis (3), was nevertheless adopted by others and has come to stay. This condition is said to have been unknown in man up to 1908. A case was reported by Ritchie as early as 1905 (4) which, though apparently unknown to the author, seems in retrospect to have been a case of complete auriculo-ventricular heart block with auricular flutter. The ventricular rate in this case was approximately thirty-five and the auricular rate approximately sixty-six a minute. Atropine was administered daily for several days. On the third day, the auricular rate was found to have risen suddenly to 275 a minute. This persisted for a few days and recurred several times thereafter. The patient was observed for six years and was reported again in 1910 (5) when the rapid auricular rate had become stabilized and had persisted for two years. The patient was said to have been comparatively well, his general health having been "better than six years ago." Polygraphic and electrocardiographic studies revealed a rapid, regular auricular contraction of approximately 275 a minute with but very slight variations when given atropine. It was at this time that the authors first adopted the term "flutter" and stated "we

prefer to term the condition of this patient auricular 'flutter' rather than fibrillation."

Hertz and Goodhart (6) are credited as having been the first to call attention to auricular flutter in man. Theirs was a case of auricular flutter in a thirty-nine year old patient with rheumatic cardiac disease. Curiously, although auricular flutter is depicted most accurately by the electrocardiogram, the diagnosis in their case, the first recorded in man, was made clinically without the aid of the electrocardiogram. Numerous tracings taken from the jugular vein, they reported, showed "an exceedingly rapid but absolutely regular pulsation." These tracings "represented genuine auricular contractions." They maintained also that the auricular beats could be seen under the fluoroscope, that they could at times be heard with the stethoscope, and that, in their case, the fine venous pulsations were seen in the retinal veins.

The most remarkable feature of their unique case, they emphasized, was 1) the extreme rapidity of the auricular contractions, 2) their regularity, and 3) their constancy over long periods.

Marked acceleration of the auricles was not regarded as uncommon and was in fact well known to workers at this time. These were, however, the auricular tachycardias and auricular fibrillations. With the recognition of auricular flutter a new entity was brought into the field of clinical medicine which differed from all the others in one essential respect; namely, with this disorder there was usually associated some measure of block between auricles and ventricles. However, "the chief reason for separation of 'auricular flutter' as it is termed, from the simple forms of paroxysmal tachycardias" suggested Lewis (7), "is, that it is more closely related to the condition which is known as auricular fibrillation and that in many instances flutter may pass or may be forced by digitalis into fibrillation."

A very comprehensive study soon appeared on auricular flutter. Lewis (8) reported sixteen cases. Some were his own and others he collected from the literature. His observations in this study were basic and his descriptions fit the clinical picture and the graphic aspects of flutter practically as we know them today. In this report he described in great detail its clinical signs together with its arterial, venous and electrocardiographic manifestations. He set out to isolate auricular flutter as "an affection which must stand for clinical, if not for pathological, purposes, in a category of its own." He felt that the term "auricular flutter" aptly described the essential condition and served to distinguish it from an allied disorder, "auricular fibrillation."

The pulse rhythm in flutter, he pointed out, is often perfectly regular for long periods and since the auriculo-ventricular ratio is commonly 2:1, the pulse rate usually indicates a simple tachycardia from 120 to 150 a minute. If, on the other hand, the ratio is 4:1, the arterial pulse being 60 to 75 a minute, the condition may go undetected. The most confusing

pulse rhythms or arterial curves he cautioned are those in which the ventricular response is irregular, for this type of response may be confused with auricular fibrillation.

The venous curve in flutter when the ventricles contracted rapidly, he found unreliable. In cases where the ventricular response was slow the auricular waves may be distinct or even prominent. One gathers from his writing that he was not much impressed with the phlebogram. He cautioned, in fact, that they may be misinterpreted.

It was in the electrocardiogram of flutter that he made a lasting contribution. These he studied in great detail and pointed out their basic characteristics. He spoke of the auricular complexes in flutter as remarkable for their constancy of form from case to case. The resemblance in shape and amplitude between auricular cycles from case to case suggested to him "a distinct and special auricular mechanism." This, some years later, he actually proved to be the case. The auricular wave in lead I he pointed out was either a small pointed summit or so small and insignificant that it cannot be found, while in leads II and III, he stated, "it runs on either side into adjacent complexes, so that a series of such complexes form a continuous wavy or zig-zag line." The auricular complex, whenever the onset can be defined, he stated, is found to be almost if not quite, a purely convex summit with a relatively abrupt upstroke and a relatively more inclined downstroke.

In this group of cases, Lewis found auricular rates as low as 200 and as high as 330. In none of the records taken in the case of any patient on any one day could he find an appreciable change in the auricular rate. He noted also, what had been pointed out previously by Rihl (9), that sufficiently strong pressure upon the vagus would stop the ventricles for periods of several seconds, but had absolutely no effect upon the auricular rate.

As to ventricular responses to auricular flutter, Lewis recognized that, although a 1:1 ratio is rarely present, and, although the ventricles are capable of a rate which corresponds to the full auricular rate, yet the common response even under stress is a 2:1 A-V ratio. This is the dominant ventricular rate in flutter, the ventricles responding to every second auricular impulse. In measuring the P-R interval preceding the ventricular response, he found that it is shorter than would be anticipated in the presence of a 2:1 block. This suggested to him that the ventricles respond to the auricular beat preceding the one adjacent to the ventricular complex. So strong is the tendency for the 2:1 ratio to dominate the heart action, he pointed out, that such slight exertion as raising the arm or a few minutes' conversation, or an unexpected visit, would provoke in some patients with an irregular or slow ventricular response, a fast and regular heart action, which on relaxation would again lapse into a 3:1, a 4:1 ratio, or an irregular beat.

The readiness with which digitalis or strophanthus would increase the existing block in flutter was recognized. In this condition the heart appeared peculiarly susceptible as in fibrillation. Conversely, when the block was thus increased, atropine would reduce the block and restore the original ventricular rate. From this it appeared that the effect of these drugs was chiefly, if not entirely, through the vagi.

That flutter had a strong tendency to lapse into fibrillation and that, similarly, fibrillation would often revert to flutter, impressed Lewis. In approximately one-half of his cases, "one condition passed directly into the other." From this he postulated that the two conditions "have a similar pathogeny." His suspicion that auricular flutter had a distinct mechanism and that flutter and fibrillation were basically related disorders was soon to be confirmed by him. In his approach to the problem he was guided by certain observations of two contemporary physiologists.

One of them, Mines (10), studying what he termed "reciprocating rhythm" on the hearts of the electric ray and the frog, observed that after the application of rhythmic stimuli, the heart exhibited a phenomenon which gave the impression that not only were the beats of the ventricle caused by those of the auricle or bulbus, but that these chambers in turn were activated by the ventricle. This effect he noted also in atropinized hearts, thus excluding intracardiac vagus effects. This phenomenon of retrograde stimulation giving rise to a "reciprocating" auricular beat puzzled him. In an attempt to explain it, he reasoned that since "it was unlikely that the actual tissue which transmitted the impulse from auricle to ventricle could immediately transmit another impulse in reverse direction," parts of the auriculo-ventricular connections responsible for this must have been quiescent during the previous transmission from auricle to ventricle. It appeared to him that such parts of the bundle, having been partly blocked physiologically as a result of repeated stimulation and therefore unable to partake in direct A-V transmission, did, however, recover in time to receive the impulse activating the ventricle and to conduct it back into auricle. Such an auricular impulse he believed may again spread back to the ventricles by way of bundle fibers which did not participate in the retrograde conduction.

To test his hypothesis he devised a rather ingenious experiment. He made a longitudinal incision into an excised auriculo-ventricular preparation of a tortoise heart, cutting through the anterior and posterior walls of both upper and lower chambers thus producing a rhomboid or a "ring." The two upper arms of this ring consisted of auricular muscle and the two lower of ventricular muscle. The auricles were thus connected to the ventricle laterally in two places. At these junctions he found excitation could pass in either direction. A stimulus applied several times to a given segment, invaded successively each of the four segments in a clockwise fashion. This cycle of events "was repeated over and over again without

any further external stimulation." From this phenomenon Mines postulated that the reciprocating rhythm "may reasonably be regarded as due to a circulating excitation."

This curious to-and-fro movement in reciprocating rhythms reminded him of the appearances sometime seen in the fibrillating mammalian heart "with the difference that in fibrillation, different portions of the muscle in a single chamber, instead of separate chambers of the heart, exhibiting reciprocating rhythm."

These brilliant experiments of Mines lead to the following important conclusions: 1) That with increasing frequency of stimulation of heart muscle the wave of excitation becomes slower and shorter and that the refractory phase is shortened. 2) That if a closed circuit of muscle is provided, greater in length than the excitation wave, a wave of contraction may be set up which will continue to propagate itself round and round the circuit for an indefinite number of times. 3) That in fibrillating heart muscle in which a slow and a short wave of excitation is once started by frequent stimulation, the high frequency of repetition of its own excitations itself tends to maintain the condition.

After the result of these experiments was sent to press, Mines conducted still another and perhaps an even more instructive one. He cut rings from the auricles of large rays. A single stimulus applied to any point in such a ring he observed started a wave in each direction. The crests of these waves would finally meet and die out. On the other hand, repeated stimulation would often induce a wave in one direction only, the other side of the point of stimulation having remained refractory. Such a wave would run around the ring slowly enough to permit recovery of refractory tissue in its path. Thus the wave in such a ring of tissue would circulate and at times continue to do so for fifty revolutions or more. An interpolated extra stimulus producing refractoriness, it was noted, stopped the circulating mechanism at once.

Apparently, while Mines was conducting his investigations, significant experiments were carried out by Garrey (11). Although in Garrey's experiments rings were cut from fibrillating tissue, his conclusions in the main were similar to those of Mines'. He added that the persistence of cardiac fibrillation is, other conditions being equal, directly proportional to the size of the tissue mass involved. The form of the tissue he pointed out was also important. Long, narrow, or thin pieces recovered promptly. The narrow strips even when connected with a fibrillating mass or when faradically stimulated did not fibrillate, but beat "coordinately." Tissue rings cut from fibrillating hearts of marine turtles ceased fibrillating, but the contraction waves continued, repeating the circuit about the ring in coordinate "circus contractions."

In explaining the unidirectional path of these circus contractions, Garrey referred to experiments of others who had produced it by graded

mechanical blocking near the point of stimulation of a muscular ring. In his own experiments he claimed to have observed spontaneous physiological blocking of tissue. It was his belief that such blocks probably resulted in intramuscular ring-like circuits with resulting circus contractions and that these blocks are fundamentally essential to the process of circus contractions.

Based upon and formulated in strict keeping with the ring experiments of the aforementioned physiologists, Mines and Garrey, Lewis in 1921 (12) presented a new conception of the underlying mechanism of flutter and fibrillation of the auricles in man. His conception of the nature of auricular flutter may be explained as follows:

Suppose that a ring of muscle is stimulated at a given point and a contraction wave is thus induced. Such a wave will travel in two directions beginning at either side of the point of stimulation and as the crests of such a pair of waves of excitation advance they soon meet and form an impassible

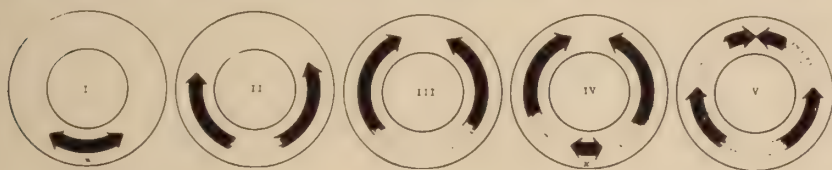


FIG. 1. In Circle I, a stimulus is applied at X, and a contraction wave is set up which travels in two directions, leaving the muscle refractory in its path as seen in II. In III, the refractoriness is shown to have begun to recover. In IV, another stimulus is applied at the original point X and a second contraction wave is seen to follow in the wake of the first. The crests of these finally meet and extinguish each other as shown in V.

barrier to each other. Thus both waves are extinguished. While the bilateral converging arc of excitation waves travel toward one another, the point of initial stimulation may have recovered and again become receptive to stimulation. Thus a second pair of waves may be made to follow the first and, in time, these, too, will extinguish each other. Single stimuli, properly timed, produce such a series of events in a ring of muscle (fig. 1).

However, when the rate of rhythmic stimulation is raised to a critical level, that is when shocks are applied to a muscle not wholly recovered, the waves thus induced may not travel freely in both directions. An area of refractoriness, a physiological block, may prevent its bilateral spread and the impulse will take a unilateral path. The crest of such a wave will advance and, meeting no opponent, will tend to make its way around the ring. If stimuli at such a moment are withdrawn and recovery of the muscle mass permitted, this circling single crest, on making its way toward the point where it started, may find completely recovered muscle in its path. If so, it will invade the area previously blocked, advance to the point of its own start and, reinvading it, begin another circuit (fig. 2). Thus, as long as con-

ditions remain unaltered, it will repeat its performance over and over again, continuing its course "as a circulating wave which has no ending." This, Lewis emphasized, is what is meant by circus movement: "it is constituted by a wave of response which travels continuously along a re-entrant path of muscle."

Lewis devised a method whereby he was able to trace the path of this circulating wave in flutter. He produced flutter experimentally in the dog's auricle by means of induction shocks applied at a rapid rate and then

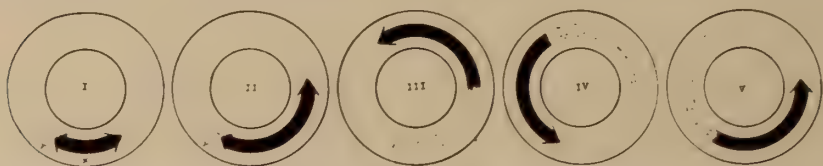


FIG. 2. In Circle I, a temporary unidirectional physiological block is indicated at point Y (dotted shading). A stimulus applied at X can travel, therefore, in one direction only, as shown in II and III. In IV, the contraction wave having completed its circuit (Y having meanwhile recovered) reenters the point where it originally started, passes it and continues (V) as a self-perpetuating ring of excitation as long as there remains a gap of receptive (recovered) muscle in its path.

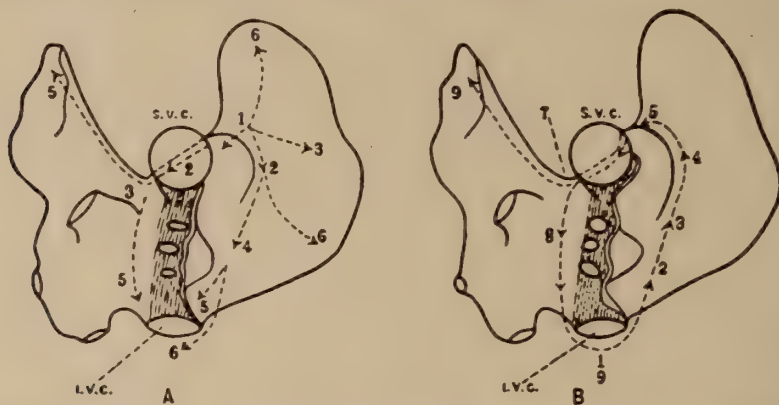


FIG. 3. Diagram of posterior portion of auricle. A, order of excitation when impulse spreads normally from S-A node to right and left auricles. B, order of excitation in "circus movements" during flutter. (After Lewis).

suddenly withdrawing them. Flutter having been established, he connected galvanometric recorders to three points chosen in the line of the *taenia terminalis* and recorded the action currents of these points simultaneously. As the excitation wave passed beneath these chosen points, their passage being signalled by the recorders, a curve had been produced which showed that each wave was passing regularly from the region of the inferior vena cava, up the *taenia*, to the region of the superior vena cava. The dimensions of the area of muscle mass having been measured, the rate at which the impulse travelled was also determined (fig. 3).

This experiment demonstrated that the path of the circulating wave in flutter is within a natural ring of muscle formed by the orifices of the two venae cavae. The circuit in the dog's auricle, represented in the diagram, was completed in 0.16 second, so that 380 circuits wave traversed each minute. The closed, central or re-entrant path is, however, not invariable. Sometimes the course in flutter is different or the course may be reversed. In some cases the excitation wave may travel in shorter paths as, for instance, around the mouth of a single cava or around some other natural

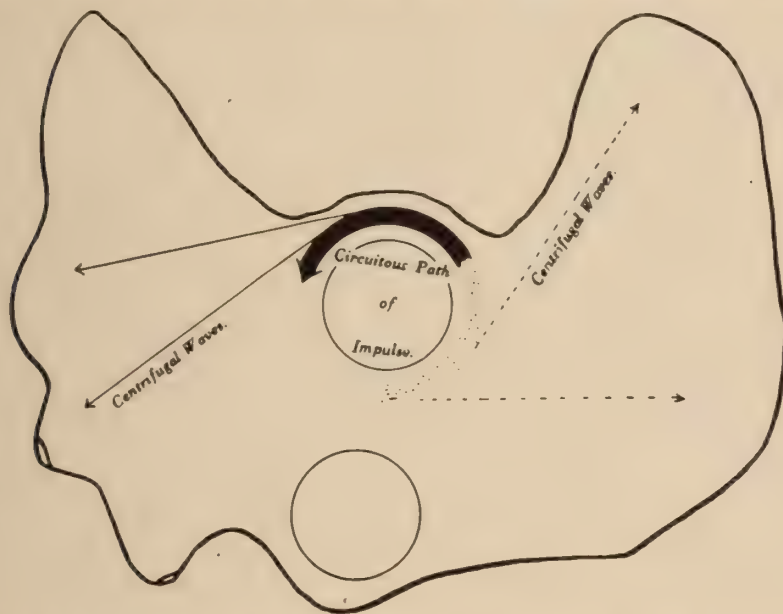


FIG. 4. A schematic diagram representing a mass of auricular muscle within which there are two available circuitous paths suitable for the mechanism of circus movement. A wave of excitation is seen to travel in one of these paths (it may travel in either of the two or in both paths). In its course, the central ring of excitation, "mother ring" sends centrifugal impulses to the adjacent musculature activating it to contract with a tempo corresponding to the rate at which the circus movement traverses its path per minute.

orifice where the architecture of the musculature is such as to favor this mechanism.

The excitation wave, of course, is not confined to the central or re-entrant path alone. Offshoots or centrifugal waves spread from the central or "mother ring" peripherally into all other regions of the auricular musculature way out to the tip of their appendices. Thus the whole mass of the auricles is set into rhythmic contractions corresponding in tempo to the number of circus movements completed per second (fig. 4). Once this mechanism has been set up experimentally it was observed to continue for hours. In the human, we know, it may continue for years.

The basic condition in the perpetuation of a flutter mechanism is that there always be, in the path of the crest of the circulating wave, a recovered or physiologically receptive "gap" of muscle. The factors upon which this depends are: 1) the length of the path, 2) the rate of advance of the impulse and 3) the duration of refractoriness of the auricular muscle. Clearly, if any of these factors are sufficiently altered, that is, if the path becomes shorter, or the circulating impulse travels faster, or if recovery of muscles is delayed (increased refractory period), the necessary gap of adequately responsive tissue for the impulse to invade cannot be maintained. Under such conditions the mechanism must come to a close. This so-called gap was destined soon to attract a great deal of attention for it was at once obvious that if by any therapeutic means such a gap could be eliminated, clinical flutter and its close ally, fibrillation, could be brought to an abrupt termination.

The close relationship between auricular flutter and auricular fibrillation, suggested not only by their several clinical similarities but also by the fact that one commonly passed into the other or could be forced into it by means of drugs, led to the belief that in auricular fibrillation, as in auricular flutter, circus movement is the underlying cause. In fibrillation of the auricles the total irregularity is not confined to the ventricles alone. The auricular mechanism, though it resembles that of flutter in many respects, is also essentially irregular. In contradistinction to flutter the auricular oscillations in fibrillation of the auricles are some fifty per cent faster and, except for short stretches, the cycles are not accurately repeated. Change is the rule.

In his attempt to decipher the auricular mechanism in fibrillation, Lewis pursued experiments similar to those in flutter. He found it impossible, however, to present an analysis quite so convincing as in flutter. The contacts which he placed on the fibrillating auricle signalled irregularly. A few impulses even failed to arrive at their proper destination. The experiment indicated not a constant path like in flutter, but a rather sinuous, changing and shorter pathway. This he attributed to a greater degree of partial refractoriness in the path of the advancing crest of the excitation wave. He believed that the gap was very small and that within it recovery was very uneven, fractional as it were. The advancing crest would therefore burrow through a sinuous path, in a "staggering fashion," setting into contraction stray fractions of muscle-bundles in its path. The path or central track traversed by the impulse in fibrillation, thought Lewis, may be a wider band of tissue than in flutter, but "the track is coarsely sinuous . . . it is a road of many and serious obstacles."

It is quite possible that this is not the whole story. It seems reasonable and not too fanciful to suppose that the mechanism of auricular fibrillation has still another feature.

The impulse, staggering as it were, in a broad sinuous path to which it is generally confined, seems to escape from time to time into a shorter circuit.

Such short circuits may be adjacent to, or a part of, the dominant path because the corresponding oscillations, though frequent, (up to 500 a minute) are generally well defined and tend to be repeated periodically. There are indications also that several small circuits may be invaded simultaneously leading to interference phenomena or that a part of the impulse may completely escape into bypaths from which it does not return. This is indicated by oscillations that are shallow, jumbled, and of a frequency far beyond the rate of any mechanism which might be assigned to circulating rhythm in man (fig. 5).

At any rate, circus movement is seemingly the basic mechanism in fibrillation as well as in flutter, the two differing essentially in that the circuits in fibrillation are shorter and more inconstant. The number of impulses which arrive at the A-V node in fibrillation are far greater than in flutter and they are irregularly spaced. The responses of the ventricles, with the exception of cases of complete A-V heart block, therefore, are fundamentally irregular.

Aside from the circular arrangement of the musculature at the natural orifices of the auricles, the rate of the oscillations in flutter themselves suggest that in attempting to locate the actual paths of the circulating waves, we must look to these natural orifices as the muscular pathway.

The auricular rates of flutter in man, Lewis found to vary from 240 to 350 a minute. In fibrillation they are about fifty per cent faster. According to these limits, the duration of a circulating wave in flutter would be 0.25 to 0.17 second. If we assume a rate of transmission in flutter as about 500 millimeters a second, the length of the path would vary between 125 and 85 millimeters. Diameters of corresponding circles would vary between 4 and 2.7 centimeters. These dimensions, assuming the transmission rates are correct, would nearly correspond to the diameters of the chief orifices in the auricles.

In the case of auricular fibrillation, the rate of movement being much faster, similar calculation would suggest that the path of the circuit is much shorter. The diameters of circuits for a circulating wave at a rate of 450 a minute would just about exceed 2 centimeters in length.

While physiologists were investigating circus rhythms, a mechanism which was finally proposed as the underlying cause of auricular flutter and fibrillation in the human heart, other workers were attracted by the effect of certain cinchona derivatives on the clinical course of these disorders. Wenckebach, in 1914 (13) reported two cases in which quinine presumably brought fibrillation of the auricles to an end. Stimulated by these observations, Frey, in 1918 (14) undertook the study of the cinchona alkaloids and their effect on auricular fibrillation. He found that quinidine, a dextro-rotary isomer of quinine, was the most effective member of the group. He reported ten cases in which, by the use of quinidine, he was able to restore normal sinus rhythm in six of them.

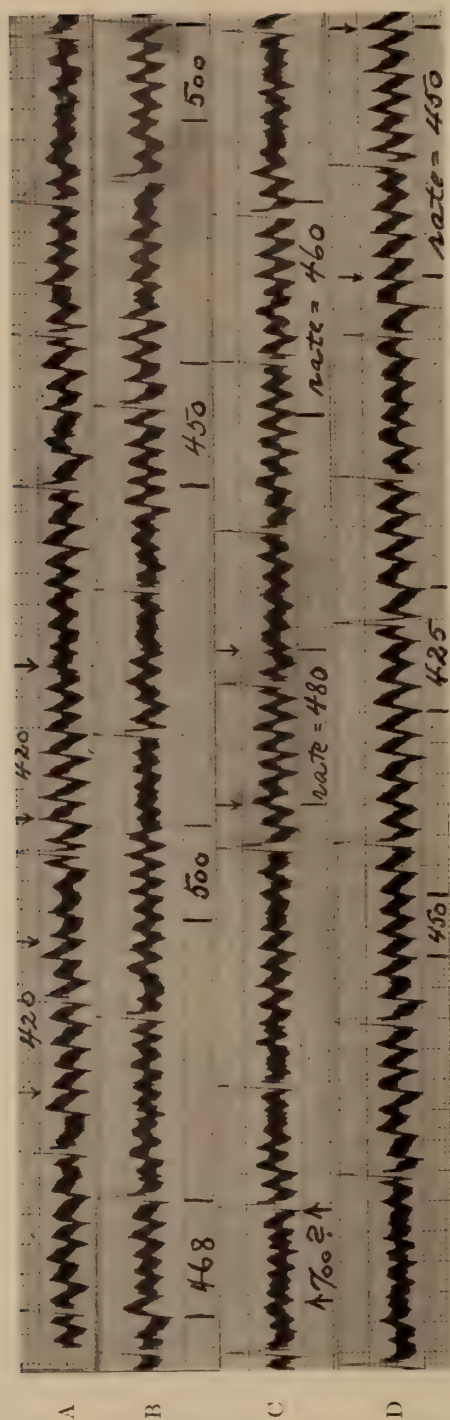


FIG. 5. Electrocardiograms A, B, C, and D are sections cut out of a long continuous tracing recorded by means of a right pectoral lead in the case of a twenty-six year old patient with rheumatic cardiac disease with a well-defined mitral and tricuspid valvular defect and auricular fibrillation.

The tracings (the first 6 cycles in A and the last 7 cycles in D) show that in auricular fibrillation, as in flutter, there is a fairly well-defined dominant circuit in which the impulse tends to circulate. That the path is short and sinuous, is indicated by the rate (420 to 450 a minute) and the changes in the configuration of the auricular complexes. Cycles in tracings B (1, 3, 5, 7) and C (4, 6, 7) indicate that the impulse has been shunted into shorter channels (rate, 450 to 500 a minute) where they persist for short periods only. Cycles A, 7; B, 2; and C, 1 show a still more rapid auricular activity but the complexes are poorly defined. In C, 1 seven oscillations can be identified in the course of 0.6 second, corresponding to a rate of approximately 700 a minute. These probably represent excitation phenomena in several synchronous circuits or bypaths, with interference.

These tracings may at first glance appear to represent "impure flutter". However, the rate of the auricular mechanism which is never below 420 a minute and the inconstancy of form of the auricular complexes obviously rule out this mechanism.

Frey's observations were soon confirmed by others. In the course of the next three years there were at least a hundred cases reported in the literature. Of these, approximately fifty per cent yielded to quinidine. As experience accumulated, successive reports began to deal with the effects of the drug, and its indications and contraindications were pointed out. Reporting his own observations and those of his collaborators, Lewis in 1922 (15) summarized existing knowledge, carefully appraised the therapeutic value of the drug, listed its known adverse effects, and pointed out precautionary measures.

Although careful observations have been recorded on the clinical and graphic aspects of the period of transition from fibrillation to flutter and to normal rhythm effected by quinidine, the actual mechanism of the restorations of sinus rhythm was not understood at this time. However, with the advent of the theory of circus movement explaining the cause of clinical flutter and fibrillation, certain features of the effects of quinidine suggested that this theory might also explain the mechanism of restoration of normal sinus rhythm (16).

In studying the effects of quinidine on the dog's heart, two important reactions stood out. The drug given in therapeutic doses per kilogram of body weight produced conspicuous lengthening of the refractory period, fifty to one hundred per cent. Its further action was a slowing of conduction in the auricular wall, this also approximately fifty to one hundred per cent. If the theory of circus movement is correct, namely, if the auricular contractions are due to a circulating excitation wave which continues in its path by virtue of a gap of recovered muscle, the two reactions mentioned as resulting from quinidine, should profoundly influence this mechanism. Lengthening of conduction time slows the auricular rate, permits recovery in the path of the circulating impulse and thus favors the perpetuation of the mechanism. Lengthening of the refractory period, though tending to eliminate the "gap" by reducing the area of recovered muscle, may for a time fail to eliminate all gaps. The primary effect of this property of quinidine is to close small circuits and to shunt the impulse into longer channels, thus also slowing the auricular rate. This is perhaps the main reason why quinidine does not always terminate auricular fibrillation. It is only when the effects of quinidine on the refractory phase of the auricular muscle outweighs its effect on conduction, it is only then, that the circus movement finally tends to come to a close.

Conditions which tend to close the gap in front of the crest of the circulating excitation wave are several: A shortening of the path, an increase in conduction rate, or an increase in refractoriness may close it. However, in quinidine therapy the first two are inconsequential and may be disregarded. The path, as a result of quinidine, actually tends to become longer because the impulse escapes into longer channels; conduction is known to become slower. Closure of the gap, therefore, which means the ending of the circus

movement would receive adequate explanation as a result of quinidine only from lengthening of the refractory period. Knowing this reaction to be always present, though not always sufficiently dominant to outweigh the accompanying reaction of slowed conduction, we can understand and can anticipate certain clinical results which we often witness during quinidine therapy. Knowing this, we can understand the clinical discrepancy of an abrupt termination of the disorder in one case and the complete failure of quinidine to terminate it in another.

The reaction of the heart to quinidine actually serves as a test for the theory upon which we have based our conception of the mechanism of auricular flutter and fibrillation. In experimental circulating rhythms it was postulated that a decreased refractory period is essential to their genesis as well as to their perpetuation. Interference with muscle recovery by mechanical means or by electric shock was found to terminate the mechanism. In the intact heart, experimental or clinical, quinidine has been found to produce a physiological block by increasing the refractory period, and to terminate the mechanism of circus movement. These observations on the action of quinidine harmonize remarkably with the theory of circus movements. This accord offers strong circumstantial evidence that the theory advanced to explain the underlying cause of auricular flutter and fibrillation is a sound one. Finally, quinidine served not only to test and more firmly to establish this theory, but also brought to the clinician and investigator valuable confirmations of old conclusions. "One of the most striking of these," states Lewis, "is its final proof that fibrillation and flutter are fundamentally similar."

The theory of circus movement may well be deemed as a major contribution of physiology to medicine. The results of its application in the solution of problems in the diagnosis and treatment of auricular flutter and fibrillation clearly indicate that in collaboration with physiology, clinical medicine is destined to solve many of its most important problems. Such collaboration should be a major aim in medicine.

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AVIATION MEDICINE

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History will probably label the first half of our twentieth century as the "Motor Age" or the "Flying Era." Much will be said about the automobile, and still more about the invention and perfection of the airplane and the evolution of aviation. These developments will be cited as epoch-making triumphs in the field of engineering and aeronautics, while the role of the pilot and of the medical man who rendered him competent in an environment otherwise lethal, will receive but scant attention.

The conquest of the air depends on two factors, the plane and the pilot. The efficacy of the plane is limited to the efficiency of the pilot, i.e., to his ability to make the machine do his bidding at all times and under all circumstances. Hence the development of the flier is as essential as that of the plane.

The development of the airplane in reality has been marvelous beyond belief. We have now a machine that can travel 575 miles per hour, can climb to 52,000 feet, can carry literally tons of explosives and can encircle the globe. The airplane at present constitutes not only the "eye of the army," but also the most destructive war weapon known to mankind.

An overwhelming preponderance of time, effort and expense has been directed to the development of the machine; by comparison, lamentably little attention has been given to the flier who must control it. Yet every great mechanical success has made additional demands upon the pilot and created for him new and unique problems which must be solved before the ultimate effectiveness of the plane can be realized.

Here aviation medicine has stepped in and undertaken the study of the problems confronting the pilot, the demands made on him physically, psychically and mentally, on all of his organs and vital senses, especially on sight, hearing, equilibrium, and on his nervous system. Through understanding based on accurate knowledge, aviation medicine attempts to select as cadets only those candidates best adapted to flying and fighting, to assign wisely to each individual pilot the tasks he can best perform, and to keep each and every flier at the peak of his efficiency at all times and under all conditions. The problems facing the pilot and his medical advisers are numerous, baffling, and often difficult of solution.

Accidents and Deaths: In the last war accidents accounted for most of the deaths in the air service and the figures are rather appalling. Three

pilots were killed in accidents for one killed in combat. In the Italian service the ratio was still worse, 5 to 1. For every four of our flying personnel arriving at the front, one cadet had succumbed to accident in training. Disease was responsible for less than 1 per cent. Accidents accounted for 75 per cent of the 681 deaths in the air service; combat for less than 25 per cent.

The cause of accidents may be divided into mechanical imperfections of the plane or motor, bad flying judgment of the pilot, and unfavorable weather conditions. The first problem belongs to the engineer; the second to the medical and training departments of the air service.

Accidents may be divided also into avoidable and unavoidable types. Thus in one field in France some 15 cadets succumbed to accidents in the month of October. In 10 of these accidents, one or more causes were assigned, 8 were adjudged avoidable. Aviation medicine can and should prevent most of the accidents of the avoidable kind.

Among other factors, lack of physical fitness, actual illness, and the effects of drugs, of too much tobacco and occasionally perhaps of alcohol too, were responsible in some instances. Cadets who were sick and failed to report it, who indulged in self-medication, who sometimes took as much as 60 grains of aspirin at a dose, went up in their planes and often crashed because of poor flying judgment and of faulty control.

Why were fatal accidents so common during the last war? Necessity was the "Mother" of aviation accidents. The immediate and imperative need for combat pilots at the front was probably the chief cause of "crack ups" in training. Pilots were demanded; hence the tempo of training had to be accelerated. Despite precautions, the incidence of accidents increased. Because of the stress of need, safety in training was sacrificed to speed.

What are the present conditions today relative to flying and accidents? In civil aeronautics flying is fast becoming as safe as any form of transportation. In flying schools in this country training is cautious and accidents relatively infrequent. This is the result of safer and better planes, more gradual and better training, and wiser administration. Personnel is still responsible for 41 per cent, power and structure for 30 per cent, and weather conditions for 25 per cent of the accidents.

What will be the story in the event of war? Shall we again be compelled to sacrifice safety to speed? Only forethought and preparedness can prevent a repetition of the losses our service suffered in the last war. It is essential for us to realize that pilots cannot be trained hurriedly except at a frightful cost in both lives and planes.

The Problem of Altitude: This constitutes one of the most important problems facing the aviator. Man is designed to live, breathe and function on the earth's surface, and not to soar above it in the heavens. Unbelievable as it seems, if we were to be gently lifted some seven miles into

the air, through the photosphere into the stratosphere, we would all become unconscious and promptly expire because of lack of oxygen. Even at two-thirds of this height most of us would become ineffective and irresponsible, even if life and consciousness were spared.

As we ascend from the sea level, the problem of oxygenation becomes more and more acute. At 3,000 feet breathing is increased; at 12,000 feet the intake of air is doubled, at 20,000 to 30,000 feet gas begins to bubble out of the cerebrospinal and other body fluids, and at 25,000 to 30,000 feet, gases may separate out from the blood and lead to serious and perhaps fatal air traps in the circulation. The R.A.F. advises the inhalation of oxygen at 16,000 feet. With the administration of oxygen man can go up to 44,000 feet, but the airplane can do much better. The airplane can ascend to more than 50,000 feet and balloons to much higher levels. Even with oxygen man is frightfully outclassed by the machine, unless he travels in specially constructed suits or is enclosed in a compression cabinet or chamber.

Aviation medicine concerns itself with the effects of lowered oxygen tension, with the reactions of the pilots, and with the best methods of supplying oxygen. At sea level air pressure is 760 mm. Hg. Oxygen partial pressure is 160 mm. Hg. When 50 mm. Hg. oxygen partial pressure is reached, most people are in dire distress, but at the lower limits of the stratosphere, the partial pressure is only 35 mm. Hg., which is too little to sustain life and consciousness. In one flight to 33,000 feet, two of three pilots died.

Even at relatively low levels many pilots become incompetent. In the last war this problem was carefully studied by aviation medicine. Artificial flights are made possible by a decompression chamber in which the pilot sits as the air is carefully and cautiously exhausted, or by means of a "Rebreather," a relatively simple apparatus in which the pilot exhausts the oxygen supply himself, by the simple process of re-breathing. Under these experimental conditions a pilot's ceiling can be determined in advance, i.e., at what height competence begins to fail. Of the pilots so examined in the last war only 61 per cent in our service were competent above 20,000 feet, 25 per cent could not function above 15,000 feet, and 14 per cent were not permitted to go above 8,000 feet.

What happens to fliers as they approach or transcend their individual ceilings? They develop shortness of breath, muscular weakness, often accompanied by marked twitching or spasm of the muscles. Though euphoric, judgment becomes deranged, muscular effort uncertain and faulty, so that the pilot is no longer competent to observe, think, or act. Headache develops, a dazed condition supervenes, then fainting occurs with unconsciousness, and sometimes coma and convulsions prior to death.

What can medicine do? By supplying oxygen in adequate amounts, all these symptoms can be overcome and the pilot can be restored quickly to normal, so that again he may think and act promptly. Oxygen may raise

his ceiling by 10,000 to 15,000 feet. It may be given by tube or by mask, the best of which in this country is that devised by Boothby and Lovelace.

Why do aviators have to fly so high? The flier with altitude has all the advantage in aerial combat. He can hover over and swoop down on his enemy at will. In addition, anti-aircraft fire now may reach to 30,000 feet, hence pilots must fly above this level to be out of range.

With adequate oxygen supply in a specially constructed cabinet or chamber, pilots may be quite comfortable at even much greater heights. Thus Major Stevens tells me that he was entirely comfortable so far as breathing was concerned at a height of 72,345 feet, the highest altitude yet attained by man. Oxygen in concentrations double that of normal was supplied above 18,000 feet. Thus it would seem that aviation medicine must now face constantly greater altitudes and perhaps also the problems of keeping pilots competent for combat in the stratospheric levels.

Altitude and Cold: Atmospheric temperature decreases 3.5°F. for each 1,000 feet. At 36,000 the temperature is minus 70°F. and above that, almost constant. At high altitudes pilots have to be prepared to resist cold as well as lack of oxygen. Masks, goggles, gloves, etc., must be considered accordingly.

The Problem of "G": Acceleration and "G" is a new problem appearing and increasing in importance, *pari passu*, with increased speed of flying and diving. A bombing pilot dives for some thousands of feet, then suddenly "pulls up in a zoom". At the beginning of the zoom his weight as expressed by pressure may have increased 9 to 10 fold. What has this done to all the tissues and fluids of his body? Blindness and even momentary unconsciousness may result. Likewise at such speeds change of motion in any other direction may result in somewhat similar effects. A sudden swerve in an automobile may be very disconcerting to the occupants of a motor car; but what happens if this swerve is effected in a plane at a speed of 400 to 500 miles per hour instead of at 40 to 50 miles? Even a slight departure from the straight line may result in momentary blindness. Ways and means are being sought to prevent this "blackout" and to protect the pilot in this moment of stress from accident and injury.

Staleness and Flying: Staleness in flying constituted a major problem in the last war. Cadets and pilots became fatigued and "fed up" at times. The quality of performance was lowered sometimes to the level that flying became actually dangerous for that particular individual. As a rule "grounding" for two to three weeks, with rest and change of environment sufficed to restore the flier to good health and to flying efficiency.

Decompression Illness: During the present war the most important problem facing the flying personnel is "Decompression Illness". This appears in pilots after prolonged frequent flights at high altitudes of more than 30,000 feet, and develops irrespective of whether or not they have inhaled oxygen. The symptoms are protean and bizarre, but include such

phenomena as nervousness, irritability, excessive fatigue, apprehension and paresthesias, and also aches and pains in the bones, joints, and muscles, symptoms somewhat suggestive of the "Bends" encountered in "Caisson" or "Compression Disease." Apparently this decompression syndrome combines many of the clinical manifestations of the old time staleness, of altitude sickness, and of Caisson Disease. The sudden and excessive pressure changes to which the pilot is exposed may well be the etiological factors concerned. Under any circumstances, this "Decompression Disease"¹ constitutes the most pressing problem demanding medical investigation at the present time.

The Eyes: Good eyes are absolutely essential in the air service. Vision must be normal in both eyes, as must also muscle balance and convergence, since the latter are easily deranged by oxygen deficiency, though readily corrected by its administration. Glasses may improve normal vision as much as 50 per cent. Obviously fogging of glasses must be avoided. Since the pilot's eye becomes the "eye of the army," his vision must be keen, accurate, and unobstructed.

The Ears: Hearing must be normal and the Eustachian tube patent. In diving unless the Eustachian tube functions easily, pressure may become so great as to burst the ear drum. Swallowing, yawning or screaming are utilized at times to force the tube open.

Equilibrium: Individuals who are hypersensitive to motion, i.e., seasick, car sick, swing sick, are apt to be air sick also. If air sickness fails to yield to proper training, the pilot is next to useless. Some can surmount this difficulty. One of our leading aces in the last war is reported to have been an air sick type during training. Overcoming this handicap, he became one of our greatest fighters. However, in the selection of fliers, those hypersensitive to motion are to be avoided.

The Brain and Nervous System: The brain and nervous system obviously are subjected to serious stresses and strains of various kinds in flight and aerial combat. They must be organically sound for admission. Both the R.A.F., and the R. C. A. F. emphasize sportsmanship in the selection of fliers, claiming that those who excel in football, cricket, baseball, etc. must of necessity possess those qualities of body and mind essential to good flying and success in combat. Sportsmanship also connotes a competitive spirit. Psychically the pilot must be of a type to welcome any challenge in flying or fighting. The "will to win" and the "Esprit de corps" are all important. In the R. A. F. they must be considered largely responsible for the failure of the German "Blitzkrieg" against England.

However, despite all our knowledge and despite the best efforts on the

¹ Special studies in this field have been carried out by the London Association for War Research under the direction of Flight Lieutenant Evelyn. From these studies it is evident that other factors besides barometric pressure are concerned. It is questionable whether the term decompression disease is a satisfactory one.

part of all those best informed about, and responsible for, the selection and training of pilots, a rather large proportion, probably 25 to 30 per cent of those accepted, fail to develop into good fliers. This failure in itself constitutes a real challenge to all those now interested in aviation medicine.

Schools of Aviation Medicine and Flight Surgeons: Two outstanding schools of aviation medicine now function in this country, one for the Army at Randolph Field, and the other for the Navy at Pensacola. Thoroughly familiar with the problems and needs of aviation, the officers constituting the faculty give training to acceptable physicians in all matters pertaining to the selection, training and maintenance of health and efficiency of the pilots. Graduates of these schools become "Flight Surgeons" and are assigned to live with pilots, share their lives and problems, and help them to keep fit and alert physically and mentally. Flight surgeons in turn accompany pilots on flights and thereby learn first hand and from personal experience the nature of the problems, hazards, and needs of the fliers.

The Need for Research in Aviation Medicine: In times of national emergency a great people will always arise to meet the occasion. As a matter of fact, most of what is now known about aviation medicine was learned in the last war, and learned because it was essential to success. Now another emergency faces us. New problems have arisen. More information is required. The time to act has come again, and we as medical men again must do our share.

But in times of war other and equally important needs also present themselves. Our schools of aviation medicine and our Flight Surgeons are taxed to their full capacity to meet just the expanding routine needs of the air service. Thousands of young men must be given careful, detailed and time-consuming examinations. The ever increasing personnel must be afforded special medical supervision. New Flight Surgeons must be trained and assigned. In other words, an imperative need for routine makes research most difficult at the very time it is needed most urgently.

Under such conditions two steps would seem to be in order, 1) the creation of a special research organization by the air service, such as that which functioned in the last war in Mineola, and in the 3rd A. I. C. in France, and 2) the creation of special groups of physicians and scientists interested in research for the prosecution of investigations bearing on aviation medicine in various scientific institutions throughout the country. Such groups already exist in a small way in England and Canada,² and to a more limited extent here in our own country. They could be developed *in extenso* and could undertake to study all the more serious medical problems facing aviation.

In view of the importance of the air service and in the face of the obvious lag in the development of the pilots as compared with the plane, the need

² During 1940, the author helped to organize such a unit in London, Canada and for a time served as its Director.

for more research in aviation medicine is obvious. Hence it behooves medical and scientific investigators at this time to turn their attention to some of these problems of aviation medicine.

From the foregoing it is evident that aviation medicine can now contribute much to the welfare of the air service. It is vitally concerned with the selection of the flier, with his physical and mental care, with his education and training, and with the solution of the unique problems incident to his calling. In the Air Service aviation medicine to date has already prevented hundreds of deaths. In addition, the principles taught and the practices it introduced have saved literally thousands of lives among those who travel by air. With the passage of time and the more universal adoption of flying the magnitude of the service of aviation medicine will become increasingly greater. But for optimal results and to meet immediate demands, more and more research is needed and needed most urgently.

HYPERTENSION ASSOCIATING UTERINE FIBROIDS: CONSIDERED FROM VIEWPOINT OF ETIOLOGICAL CONNECTION AND SURGICAL RISK (BASED ON REVIEW OF 500 CASES)

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Hypertension has generally been considered a serious handicap to the patient with fibroids which produce symptoms severe enough to warrant operative removal. In such cases the element of risk incidental to hysterectomy is considered an important factor in formulating the indication for surgical intervention. In certain instances of hypertension more conservative procedures have been adopted in order to avoid the allegedly increased hazards of operative shock and postoperative complications.

Not infrequently x-ray therapy has been resorted to as a substitute for hysterectomy in cases of fibroids associated with hypertension, notwithstanding the fact that in instances of submucous myoma it promises less certain therapeutic result than can be obtained by surgery. Following x-ray treatment the submucous myoma may become torn away from its pedicle attachment and through vascular deprivation become necrotic giving rise later to serious hemorrhages. Radium has the disadvantage of producing necrosis by direct action on the submucous myoma.

The malignant variety of hypertension has been regarded as the most serious condition associated with uterine fibroids as it is in the presence of any other pathological condition requiring major surgery. On the other hand according to some observers the operative removal apparently has some beneficial effect on hypertension of this type.

The possibility that x-ray or radium treatment may aggravate hypertension through their destructive effects upon the ovaries is a question which has not been satisfactorily answered. It is common knowledge that menopause in general is marked by increased vascular tension. The production of artificial menopause in the presence of hypertension would therefore appear to be undesirable. Against this disadvantage hysterectomy offers the possibility of retaining the ovaries thus postponing in the majority of instances the onset of menopausal disturbances.

In view of these considerations it was thought desirable to review 500 cases of fibroids which came to operation and to note the incidence of accidents, mortality and complications that may be attributed *per se* to the hypertension. The series consisted of unselected and consecutively operated cases from the gynecological service of The Mount Sinai Hospital.

Of the 500 cases there were 67 with a minimum blood pressure of 150 systolic and 90 diastolic, and pressures exceeding the latter which are generally accepted as criteria of hypertension. In view of the natural incidence of hypertension being proportionate to advancing years the cases were divided into age groups according to decades.

In the age group of 20 to 29 there were 51 cases of fibroids without a single hypertensive patient. Despite ten per cent of the fibroids occurring in the third decade of life no case of hypertension was encountered. In the group of 30 to 39 years there were 228 cases of fibroids, 11 of which showed hypertension (4.8 per cent). In 6 cases the blood pressure ranged between 150 and 159; in 4 cases 160 and 169; in one case 230. Although constituting almost half the total number of fibroids (45.7 per cent) hypertension of this group aggregated 16.2 per cent of the total number of hypertensive patients.

In the fifth decade of life there were 188 cases of which 39 were classified as hypertensives. The percentage was 15.4. In 17 cases the pressure ranged between 150 and 159; in 9 cases 160 and 170; in 5 cases 170 and 180; in 5 cases 180 and 190; in one case 190 and 200; in one case 210 and in another case 230. In the sixth decade of life there were 41 cases of fibroids with 12 hypertensives, a percentage of 29.2. In 4 cases the pressure ranged between 150 and 159; in 2 cases 160 and 169; in 2 cases 180 and 189; in one case 190; in 2 cases 200; in one case 220 systolic and 120 diastolic.

Above 60 years there were 5 cases out of 10 (4 from 60 to 69 years; and one 73 years old) all of whom were classified as hypertensives. This group is too small to deduce any conclusions; hypertension is obviously expected to be highest beyond the sixth decade of life. In the group from 60 to 69 years the blood pressure in one case was 140 systolic and 100 diastolic; in 2 cases, 162 to 165 systolic and 104 and 90 diastolic; in one case 190 systolic and 100 diastolic. In the group of 70 to 79 years the pressure was 175 systolic and 105 diastolic.

The incidence of hypertension associated with uterine fibroids met with in the fourth, fifth, sixth and seventh decades of life corresponds in general with the occurrence of increased arterial tension in larger groups of women of the same age periods. Of special significance is the absence of hypertension in the third decade where not a single case of hypertension was encountered despite the fact that it constituted 10 per cent of the fibroids.

Although 500 cases are not quite enough to allow of final conclusions, they indicate, nevertheless, that there is no justifiable basis for the assumption that the presence of fibroids by themselves induce the hypertensive state or that they have any appreciable etiological bearing upon this condition.

With reference to the theoretical question of the relation between the size of the tumors and cardiovascular strain the following data are of interest. There were 13 cases with fibroids enlarging the uterus in size from

1½ months of pregnancy to 3 months; 42 cases with uterine enlargement to from 3 to 4 months pregnancy, and 10 cases with uterine enlargement varying in size from 4½ months to 8 months of pregnancy. Two cases showed uterine enlargements to about the size of full term pregnancy.

It is to be noted that the uterine enlargement was measured in terms of gestation to which, in accordance with common practice, the uterine mass of fibroids was roughly and approximately compared. Of special interest in connection with the problem of possible etiology is the fact that of the two patients with the largest tumors, in one the blood pressure was 150 systolic and 94 diastolic and the other 175 systolic and 105 diastolic.

From the viewpoint of increasing the hazards of surgery the study of these 500 cases show the following data:

Only one postoperative death occurred out of the 67 cases with hypertension. This was a patient with fibroids and bilateral ovarian adenocarcinoma. Gastric dilatation followed upon the second day of the operation and cerebral embolus with hemiparesis on the ninth day. She had had mitral stenosis and insufficiency. The neurologic consultant found symptoms and signs indicating focal involvement of the right central hemisphere. The patient died on the thirteenth day after operation.

There were 10 complications following operation in the hypertensive group (approximately 15 per cent): atelectatic bronchopneumonia in one case; pyelitis in one case; wound infection in one case; marked abdominal distention requiring Wangenstein drainage in one case. Two patients required blood transfusions because of anemia; two patients developed large exudates and one patient had postoperative fever for which no adequate explanation was found.

The complications in the non-hypertensives (433 cases) were as follows: There were 39 complications (8.3 per cent): wound separation, 3 cases; marked abdominal distention requiring Wangenstein drainage, 4 cases; wound infection, 4 cases; bronchopneumonia, 2 cases; large pelvic exudate, 2 cases; requiring transfusion 8 cases; pyelitis, 3 cases; pulmonary infarct, 2 cases; hematoma of wound, 6 cases; pulmonary infarct with atelectasis and pneumonia, 2 cases; thrombophlebitis, 3 cases. Two deaths occurred in this series.

The surgical and medical complications enumerated for the hypertensive cases showed an appreciable increase over the comparative group, but this does not appear to be traceable to the increase in blood pressure.

It is of interest to compare the duration of hospital stay of the patients in the two groups. In the hypertensive group 60 were able to leave the hospital before or on the sixteenth day (approximately 93 per cent) while the remaining 7 cases remained from the seventeenth to the twenty-first day inclusive.

Of the 433 non-hypertensive cases, 346 were discharged on or before the sixteenth day (approximately 80 per cent); 77 patients were kept in the

hospital from the seventeenth day to the twenty-first day inclusive (17.6 per cent); 10 patients required hospitalization from twenty-two to thirty-eight days (2.3 per cent).

The period of hospitalization is of particular significance since 44 of the hypertensive cases were associated with abnormal cardiac features. These were: heart enlargement in 30 cases; mitral systolic murmurs in 6 cases; mitral systolic and diastolic murmurs in 6 cases and aortic systolic and diastolic murmurs in 2 cases.

The anesthesia consisting of a combination of ethylene and ether which was applied to both groups was equally well tolerated.

In the past four years 3 cases of fibroids were encountered which were not considered suitable for operation because of an associated cardiovascular condition. These are briefly noted.

Case 1. Age 40 yrs.; chief complaint: uterine fibroids with menorrhagia. (rheumatic cardiovascular disease). Auricular fibrillation. Blood pressure 150 systolic and 70 diastolic. Uterus size of 6 months gravidity; double mitral, double aortic murmurs. Referred for x-ray therapy.

Case 2. Age 34 yrs.; chief complaint: menorrhagia. Blood pressure 172 systolic and 70 diastolic. Uterus enlarged to size of 4 months gravidity; double mitral murmurs; double aortic murmurs. Medical consultant advised x-ray therapy.

Case 3. Age, 36 yrs. Fibroid uterus size of 6 weeks gravidity; heart enlarged; eye ground changes; malignant phase of essential hypertension. Blood pressure 230 systolic and 150 diastolic. Operation deferred.

SUMMARY

In a series of 500 consecutive cases operated upon for uterine fibroids, hypertension was encountered in 67, an incidence of 13.4 per cent. Analyzed with reference to the age groups there appeared to be no appreciable increase in hypertension which could be attributed to the presence of these uterine tumors. The review further showed that hypertension *per se* does not seriously increase the risk of hysterectomy and need not, except in the malignant type, contraindicate surgical intervention.

THE PROBLEM OF ALLERGY IN RHEUMATIC DISEASE

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Among the many problems in rheumatic disease, those pertaining to etiology and allergy are most frequently discussed; they belong together. As regards the former, it is not my intention to go into this difficult question beyond making the following few remarks. The streptococcus with its special characteristics is still uppermost in these discussions with no definite solution in sight. It is very probable now that a new means of observation has been made available by the construction of the electrone microscope that "virus studies" will be undertaken with new vigor.

The relationship of rheumatic disease to tuberculosis deserves much attention. Coronini (1) only recently published results of her studies of Tbc. bacillema, representing 10 years of work and the observations on 1800 blood cultures, with special attention to rheumatic disease. She cultured 160 strains of Tbc. bacilli, 132 of which she checked by histological examinations, and recultured from the guinea pig. Loewenstein (2) speaks of rheumatic disease as a "Paratuberculous" condition. His painstaking studies have not been accepted, although it must be conceded that many features of rheumatic disease resemble tuberculosis. There are authors who are even inclined to regard the Aschoff bodies as some kind of modified tubercles.

A great deal of controversy exists as to what type of streptococci should be accepted as the causative agent. Small (3) emphasises the cardioarthritic streptococcus, whereas Coburn (4) stresses the toxin producing hemolytic streptococci which enter through the respiratory tract. The streptococcus at best is regarded as a secondary invader in association with a virus and is considered responsible for the recurrence of rheumatic symptoms. The peculiar response of rheumatic patients to the invasion of toxin producing hemolytic streptococci is pointed out by Coburn. This peculiar response to infectious agents may not be entirely restricted to streptococci. Interesting results obtained in the study of antibodies provided by certain strains of streptococci can also be taken as proof that a close relationship exists between such streptococci and rheumatic disease.

Of importance also is the occurrence and recurrence of rheumatic symptoms in the course of scarlet fever, a disease in which a special strain streptococcus is considered as the causative factor. On the one hand it is observed that rheumatic patients seldom develop scarlet fever, indicating the existence of a certain immunity against streptococci. But, on the

other hand, rheumatic disease may begin or recur during an attack of scarlet fever, a fact which can be best explained by a form of sensitivity or an allergic reaction to members of the streptococcus family, induced by scarlet fever. It is interesting that during an intensive study of scarlet fever in Vienna, I saw endocarditis appear during scarlet fever in only six out of 2000 cases. Pospischill (5) with his wide experience in scarlet fever also drew attention to the rarity of endocarditis in this disease. These observations are more significant when it is recalled that synovitis relatively frequently appears as an early sign during the first week of the disease and that these forms of synovitis disappear without leading to valvular affliction. Therefore, I (6) was in favor of separating these forms of "synovitis" from the general category of rheumatic disease. There are also numerous cases of scarlet fever showing arrhythmia, systolic murmurs, and some dilatation of the heart. Such cases, however, cleared up entirely and, therefore, the diagnosis of a rheumatic valvular disease becomes untenable. I suggested the term "myasthenia cordis" for this peculiar heart condition.

In New York the situation is quite different. Paralleling the greater frequency of rheumatic disease in this city there are (and I saw and know of) many more cases of real rheumatic disease which have their beginning during the scarlet fever process than I have encountered in Vienna. Similar observations have been reported in England.

This would indicate that the causative agent of rheumatic disease is more prevalent in New York. It may be present in a latent form and released during scarlet fever (7).

I wish to emphasize the fact that rheumatic disease is rare among infants and infrequent during the second year of life, which may point to a transmission of immunity against rheumatic infection by the mother. This immunity, however, becomes lost after the first two years after birth, as in the case of other infectious diseases. The study of families with children showing rheumatic disease in infancy reveals significant information. Thus, there are reports of occurrence of rheumatic infection in a newborn infant of a mother suffering with rheumatism. Similarly significant is the high incidence of rheumatic disease in children of families in which the parents or relatives are suffering from this disease. This may be due partly to more intensive exposure and partly to greater susceptibility. Similar observations can be made in tuberculous families. However, it is to be borne in mind that exposure to infection is a more important factor than the hereditary influence.

With regard to the problems of etiology, I wish to point out that the streptococcus is considered to play a more important rôle in relation to the recurrence of rheumatic symptoms, than as the real cause of rheumatic disease.

With this introduction we may approach the problem of allergy. Various

observers noted the fact that a respiratory infection (particularly sinus, nose and throat infections) precedes the onset of rheumatic symptoms in the joints by about fourteen days. The fact that serum disease, sometimes accompanied by joint symptoms, has a similar incubation period leads one to the hypothesis that the rheumatic "syndrome" just as the serum disease is an allergic manifestation in reaction to a foreign protein. The protein components of the causative agents sensitize the organism; fever and other manifestations are the result of an antigen-antibody reaction. In this sense rheumatic disease does not differ from all other diseases which have a relatively fixed incubation period such as measles, typhoid fever, smallpox, etc. There, according to the theory of Pirquet and Schick, the incubation period is necessary to provide for the production of bacteriolytic and other antibodies. These antibodies either set free endotoxic substances by destroying the invading germs or create "apotoxic" substances by the interaction of protein-like substances excreted by the micro-organism or such as are present within their bodies. It is the latter mechanism particularly which comes under consideration in the case of serum sickness where one deals with an inanimate substance (foreign protein) which does not multiply.

In acute infections, the duration of the disease is limited because the invaded organism is able either to destroy the pathogenic germ in a relatively short time or make it harmless (virus). In subacute diseases this process of destruction needs more time, while in chronic diseases this defense mechanism is not efficient enough to quickly eliminate or destroy the invading germ or virus. Only some form of equilibrium may be attained with the symptoms subsiding and reappearing. Months and even years are necessary to arrest the disease. If we consider rheumatic disease from such a point of view, allergic features must be expected. I have seen several cases of rheumatic disease which were ushered in by repeated eruptions of urticaria, so that at first a food allergy was suspected. The allergic nature of rheumatic symptoms cannot be different from those in other diseases. Many authors regard the reaction of the diseased tissue as "hyperergic," mainly because it is more intensive than the usual "allergic" reaction to the repeated contact between antigenic substances and antibody. Intensive hyperemia, excessive exudation or rapidly developing edema are characteristic symptoms of such a "hyperergic" reaction. However, the two week interval between the preceding "respiratory infection" and the onset of rheumatic disease is not enough to call the disease "hyperergic" in character. If rheumatic disease in its first attack or later in its course would show very intensive exudation into the joints accompanied with intensive, general toxic symptoms it would be reasonable to consider the symptoms as "hyperergic." Indeed, in the history of rheumatic infection hyperergic forms of rheumatic disease are reported. The so-called "cerebral" rheumatic process, sometimes fatal,

characterized by hyperpyrexia and cerebral manifestations (delirium, hallucinations, coma, etc.) represents an expression of an hypersensitive organism. It is interesting to note that such forms of rheumatic disease are now rarely seen. This may be due to the attenuation of the causative agent or to the improved defense mechanism of the population.

The occurrence of such a change in the intensity of disease is known, as exemplified by lues which for centuries was frequently a deadly disease. Also the smallpox virus seems to be somewhat attenuated in the United States.

As I consider the clinical manifestations of rheumatic disease from the viewpoint of allergy, I see no principal difference between rheumatic disease and tuberculosis. There is an incubation period between invasion and the appearance of the first symptoms. In tuberculosis the first symptoms become manifest later than in rheumatic disease and are usually insidious in their onset. Tuberculosis has its acute stage which slowly subsides and eventually relapses. In tuberculosis there is the great advantage of being able to detect the presence of the disease by testing with tuberculin, while unfortunately, such skin testing is not available for rheumatic infection. All skin tests to substances derived from streptococci are as yet unsatisfactory and rather confusing.

So far the results obtained from the examination of antistreptolysin or complement-fixing antibodies have not led to any definite conclusions. In this respect it may be recalled that even in serum sickness the search for precipitin and other antibodies has difficulties. Only passive transfer yields proof of the existence of antibodies. In rheumatic disease also no antitoxic antibodies could be found. The presence of antitoxic antibodies would rather prevent the development of clinical symptoms of allergy.

In conclusion I would say that rheumatic disease produces clinical symptoms characteristic of allergy not differing from those of allergy in other infectious diseases. As a rule no hyperergic reaction manifests itself clinically.

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BILATERAL THROMBOSIS OF THE POSTERIOR CEREBRAL ARTERIES

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We are indebted to the work of Holmes and Lister (1) for the localizations of the visual functions in the occipital lobes. In 1916 they studied many cases of gunshot wounds of the occipital region and determined the representation of the peripheral and macular areas of the retina upon the visual center.

The visual center is mainly on the mesial aspect of the occipital lobe and is divided into an upper and lower part by the calcarine fissure. Above this fissure is the cuneate lobe, below it is the lingual gyrus. The visual center also extends on to the convexity of the occipital lobe at its posterior extremity. The calcarine fissure forms a boundary line between the cortical representation of the upper and lower quadrants of the corresponding half of the visual field in both eyes (2).

The visual cortex is supplied by branches of the posterior cerebral artery, while the macular area is supplied by both the posterior and middle cerebral arteries, so that if one of these vessels is blocked by embolus or thrombosis, the other will supply blood to this area of the cortex. Thrombosis of the posterior cerebral artery, therefore, causes a crossed hemianopsia with, as a rule, escape of the fixation point (3). Bilateral thrombosis of the posterior cerebral arteries causes at first complete blindness, double hemianopsia, with subsequent recovery of a small area of central vision, about five degrees around the fixation point. Occlusion of the posterior cerebral artery is most likely to take place in the cortical and especially the calcarine branches.

The onset of hemianopsia, due to thrombosis of the calcarine artery, may be accompanied by xanthopsia; one of Harris' (4) patients with hyperpiesis developed right hemianopsia, saw everything bathed in a golden light minutes before her vision failed. Holmes also quotes a case of a woman with an occipital lesion who saw golden crosses and figures.

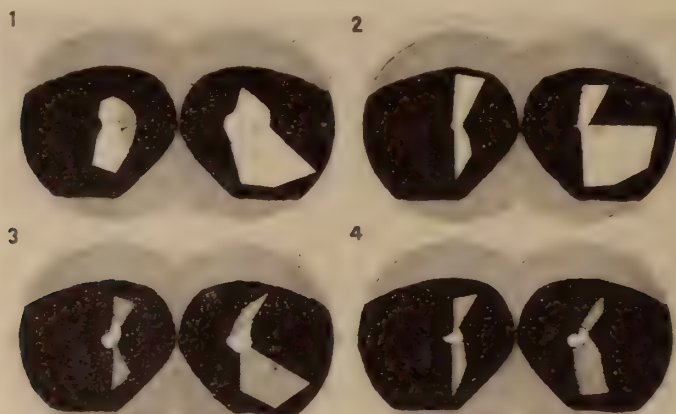
Monbrun (5) in a review of the subject states that lateral homonymous hemianopsias of vascular origin are rarely due to hemorrhage. Practically always they are the result of ischemia. Arterial obstruction may be caused by embolism, but most commonly it is due to arteritis (syphilitic or atheromatous), to which may be superadded a spasmodic element which has been occasioned by general circulatory change. In certain cases at least there is a definite sequence of stages: endarteritis with subtotal obliteration;

spasm; ischemia, which may be relative, transitory or in any event not destructive from the onset, but which will eventually become complete, leading to softening of the brain even in the absence of any total anatomical obstruction of the artery.

CASE REPORT

History. J. M., male, white, age 70 was first seen on March 9, 1935. There was a family history of diabetes. In 1914 he had a carbuncle on the neck. From 1933 he had been subject to intermittent claudication, particularly in the right leg, whenever he walked a few blocks. In July 1933 he had lobar pneumonia followed by pleurisy and effusion. Formerly he weighed 238 lbs.; in 1935 he weighed 187 pounds. The blood sugar was frequently determined and ranged between 150 and 200 mg. per 100 cc.

Examination. An obese elderly man with an emphysematous chest. His pulse was slow (60 per minute). The blood pressure was 140 systolic and 90 diastolic.



Fields: 1—December 13, 1937
2—December 24, 1937
3—February 21, 1938
4—June 22, 1938

There were no cardiac murmurs; but the heart sounds were distant. The liver and spleen were not palpable. His feet were cold and neither the dorsalis pedis, posterior tibial nor popliteal vessels could be felt on either side. The femoral pulses were excellent. The fundi showed diabetic retinitis.

Laboratory data. Urine specific gravity, 1020; no albumin; no sugar; no casts or pus cells. X-ray examination of the chest showed the heart to be slightly hypertrophied; the knob of the aorta was prominent and its edge was rather dense, indicating arteriosclerosis and possibly a little calcification. An electrocardiogram showed left ventricular preponderance.

Course. In November 1937 he had an upper respiratory infection. This was followed by a rather severe sinus attack which was treated. About that time he complained of increasing haziness of vision and difficulty in reading. He complained also that his memory had been defective. Except for absent knee jerks, which was attributed to diabetes, he showed no evidence of a neurological disturbance.

Ophthalmological history. On December 8, 1937 he was seen by his oculist in Baltimore who had observed him over a period of ten years and for several years he had

found "diabetic retinitis". The onset of his more recent symptoms was insidious. About four weeks earlier he stumbled over a step which he apparently was unable to see, and on Thanksgiving Day he complained that he could not see well enough to carve the turkey. However, he was able to continue his work for several days when he suddenly noticed a geometrical pattern before his eyes and became unable to read. This positive scotoma disappeared in a day or so but his vision did not clear. The doctor could not obtain satisfactory fields but thought he was suffering from retrobulbar neuritis due to the diabetes.

The patient was seen by me on December 13, 1937. His vision was O.D. 20/20, O.S. 20/20. The pupils reacted normally. There were incipient lens changes and a few fine vitreous floaters. Fundi: O.D. nerve head, of a fairly good pink color; arteries, narrow. There were a few fine hemorrhages along the inferior temporal vessels. There was a group of hard white exudates above and temporal to the macula. O.S. nerve head, slightly pale; arteries, narrow; there were a few fine hemorrhages about the macula. The fields of vision showed loss of all but central vision and a narrow area above and below; this was evidently the result of double homonymous hemianopsia (see fields). My diagnosis was: blocking of the blood supply to both occipital lobes.

Comment. The thrombosis may vary in extent and finally reach a stationary stage. In rare cases both sides may be affected with cortical blindness. In this condition, complete blindness is found with normal pupillary reflexes. More commonly as in this case, the macular area is spared and there is double hemianopsia with normal vision in a small central zone of the field.

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INOCULATION MALARIA AND DRUG ADDICTION

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Since the recognition of inoculation malaria among drug addicts in 1929 (1), this mode of infection, at first a medical curiosity, has become a public health problem in urban United States. It has been stated that "the present incidence and mortality from malaria in New York City is almost entirely due to the occurrence of the malignant form of the disease in the drug addict population" (2). Reports from other American cities have indicated a steadily growing incidence of malaria among addicts and observers state that many more cases could be revealed by a careful search. In this communication, two cases of malaria in drug addicts are presented to call attention once more to the remarkable clinical features and epidemiology of this infection.

CASE REPORTS

Case 1. History. R. S., a 32 year old white, married woman, entered the hospital on September 15, 1939 complaining of chills and fever. Five years before, she acquired syphilis and was given a course of anti-luetic therapy. Four weeks before admission, she developed numerous abscesses on the lower extremities and began to experience recurrent chills and fever. For one week she was treated several times in the emergency ward of the hospital and was admitted finally because of high temperature and a painful carbuncle on the right thigh.

Examination. The patient appeared acutely ill and pale. The temperature was 103°F. There was a bismuth line on the gingival margins. Teeth were dirty and carious. The lungs were clear; the heart was normal. A firm non-tender spleen could be felt three fingers below the costal margin. There were numerous ecchymoses on the arms, hands, feet and chest as well as many excoriations and fine pitted scars. On the extremities, small scars seemed to follow the course of superficial veins. There were numerous inflamed thrombosed arm and leg veins. A large furuncle was present on the right forearm and a recently incised carbuncle on the right thigh.

Laboratory data. The hemoglobin on admission was 61 per cent; red blood cells, 3,340,000; white blood cells, 6,700 with 67 per cent polymorphonuclear leucocytes: 23 per cent lymphocytes, 9 per cent monocytes and 1 per cent plasma cells; platelets were only 25,000. The blood urea nitrogen was 10 mg. per cent, blood sugar, 100 mg. per cent, total protein, 5.5 gm. per cent, icterus index, 9. A blood culture was negative. The blood Wassermann reaction was positive. The urine contained a very faint trace of albumin and occasional white blood cells. Repeated blood smears revealed malarial ring forms within red blood cells. The type of parasite was not identified. Bone marrow aspiration showed a hyperplastic marrow with an increase in megakaryocytes.

Course. Persistent questioning gained the admission that for 6 to 7 years she had been addicted to heroin and had been interned at the House of Detention on 2 occasions for treatment. She administered the drug intravenously using a hypoder-

mic needle attached to a medicine dropper. On several occasions, she became a member of a group of addicts who used a common hypodermic needle. It was not known whether any of her associates were similarly ill. The patient attributed her illness to her addiction and believed it due to a poor grade of the drug in spite of the cost of \$4.00 a day to secure the drug.

After several days of irregularly recurring chills and fever, treatment was instituted with 10 grains of quinine sulfate, twice daily for 14 days. The patient promptly became afebrile and on the ninth day of treatment malarial parasites disappeared from the peripheral blood. The hemoglobin rose to 75 per cent and the blood platelets to 235,000 per cu. mm. Leucopenia persisted, however, and during the third hospital week, the platelet count dropped to 50,000 and then to 20,000 per cu. mm. The bleeding and clotting times were normal. The capillary fragility test was markedly positive. The stools became guaiac positive and sigmoidoscopy showed a ring of small internal hemorrhoids, but there was no evidence of active bleeding. The drug addiction was controlled with small frequent doses of Magendie's solution and atropine by hypodermic injection. On discharge, five weeks after admission, the patient was no longer dependent on the drug. She began to menstruate for the first time in two years.

Case 2. History. L. W., a 34 year old, married, white woman, a vagrant, entered the hospital on January 2, 1940 complaining of recurrent chills and fever. She had had pneumonia and pleurisy at the age of twelve and a *fistula in ano* at the age of nineteen. Six months prior to her admission she had become separated from her husband, becoming a vagrant and living precariously. Three weeks before admission, she began to have nightly chills followed by fever lasting until morning. Shortly before entering the hospital, she began to experience numbness and tingling in her hands and feet. During a shaking chill, she sought admission to the hospital.

Examination. The patient was a thin, dirty, white woman of 37 in a state of physical and mental deterioration. Her temperature was 104° F., pulse 122, respiration, 36. The teeth were dirty and carious. There were sodden split papular areas at the corners of the mouth. There were occasional râles at the base of each lung posteriorly and a soft systolic murmur was heard at the apex. The liver was felt two fingers below the costal margin and a freely movable, notched spleen was felt five fingers below the costal margin. There were numerous small depressed, greenish-blue pitted scars over the arms and thighs. The veins running along the dorsum of the right wrist and lower forearm showed numerous closely set puncture marks which outlined their course. There was a diffuse shiny erythema of the skin of each leg.

The finding of puncture marks suggested the probability of heroin addiction and inoculation malaria. The patient admitted that she had become a morphine addict in 1926 and had used this drug until 1932 when she gave it up for large doses of barbiturates. Six months ago, she became addicted to heroin which she administered to herself intravenously in doses of 1 8 oz. 4 to 5 times daily. A medicine dropper and a hypodermic needle were used. On several occasions, she had used a friend's syringe.

Laboratory data. Hemoglobin, 60 per cent; red blood cells, 3,000,000; white blood cells, 1,050; platelets, 95,000; polymorphonuclear leucocytes, 50 per cent; eosinophiles 1 per cent, monocytes 8 per cent, lymphocytes 41 per cent. Blood smear revealed many ring forms of malaria; the type of plasmodium was not determined. The urine was clear, acid; its specific gravity was 1.020, and it was negative for sugar, albumin and formed elements. The blood Wassermann reaction was negative. The blood urea nitrogen was 13 mg. per cent, sugar 100 mg. per cent, icterus index, 9. An electrocardiogram was normal. The sedimentation time, was 35 minutes. The clotting time was 4 minutes.

Course. The patient was given 10 grains of quinine sulfate 3 times daily with

prompt disappearance of chills and of high spiking temperature. She smoked and whined incessantly, despite frequent small doses of morphine becoming a ward problem. She was transferred to Bellevue Hospital for further care. Her white blood count had risen to 3,100 and the platelets to 125,000 per cu. mm. Rare malarial parasites were still present in the peripheral blood smears.

DISCUSSION

The association of malaria with drug addiction was first noted in Cairo, Egypt during the most intense epidemic of drug addiction yet recorded (1). Biggam observed that many of the addicts hospitalized for various complaints who presented signs of venipuncture, thrombosed basilic veins, and fever, were infected with the parasites of malignant sub-tertian malaria. As this type of infection was exceedingly rare in that region, it was soon considered probable that they had contracted their infection by some abnormal route. Investigation revealed that the addicts had obtained intravenous injections of heroin and that no attempt had been made to sterilize the syringes between injections. This led Biggam to suspect that the route of infection was the use of common syringes which probably had become infected with the blood of a malaria carrier. In two instances, syringes were confiscated and were immediately examined for parasites but none were found.

During the ensuing year, Biggam and Arafa (1) observed more than 100 cases of malaria among addicts, many of whom were comatose and apparently suffering from a cerebral form of the disease. In others, the chief complaint resembled an intestinal affection which varied in severity from a mild diarrhea to a severe dysentery. Soon thereafter, numerous reports appeared describing malaria among addicts in non-endemic foci. Geiger (3) in San Francisco, Faget (4) in New Orleans, Himmelsbach (5) at Fort Leavenworth in Kansas, Wang (6) in Peiping, Eaton and Feinberg (7) in Chicago; Helpert (8, 13) in New York City, and others (9 to 19) reported such cases.

The drug usually employed by these addicts is heroin (diacetylmorphine), which has displaced morphine as the chief drug of addiction in many locations, notably in New York and Egypt. An inherent danger in heroin addiction to the community is that the addict becomes an extrovert and seeks the company of other habitués in contrast to the morphine addict who is a solitary introvert (20). The universal desire of the heroin addict for companionship is probably the basic reason for the spread of malaria in the group which is scattered throughout the world.

The implements used by the majority of heroin addicts in all parts of the world are surprisingly similar. A rubber-nippled eye-dropper, the tip of which is wrapped in paper and is fitted into a hypodermic needle, is most commonly employed for the intravenous administration of the drug. With the use of this implement, the danger of being "caught" with a syringe is minimized and the possibility for self-medication is en-

hanced. The drug is dissolved sometimes in an empty metal bottle cap and drawn into the dropper. No attempt is made at sterilization of equipment. The high price of the drug induces many of the addicts to pool their funds in order to buy on better terms. They then share their purchase by passing the dropper around. The needle is inserted into a vein, blood aspirated, and a portion of the dissolved drug injected. It is then passed to a partner who uses his *aliquot* in the same manner. In this way, the blood of several individuals is mixed. Should one of them be a carrier of malaria or of syphilis, he may serve as a source of infection for those who follow him.

The outfit is often left at some hiding place, such as a lavatory, cellar, or abandoned flat, and many come to use it. Therefore, one addict may have no knowledge of previous users. In a routine examination of addicts brought to the Tombs prison in New York City, Helpern (8, 13) found that 9 out of 150 addicts harbored malarial parasites in their blood. Only one of these 9 had ever been in the tropics where he could have been infected in the natural way. The 9 admitted sharing their doses freely with each other and also with many of the fatal cases that Helpern had previously studied.

Geiger (3), in 1932, while investigating 6 cases of malaria reported in San Francisco, found that 5 were morphine addicts living in the same hotel. Himmelsbach (5) was able to trace several infected addicts whom he observed at the United States Penitentiary at Fort Leavenworth, Kansas, to a group who had been confined in Chicago and who had been taking and sharing the drug. Numerous cases had been reported among addicts in Chicago (7) and several of Himmelsbach's cases had never taken the drug before. Himmelsbach also found aestivo-autumnal malaria in an addict who had come from New Orleans. Faget (4) had reported that 29.4 per cent of addicts in New Orleans were suffering from active malaria. Bradley (12) found numerous instances where addicts, ill with malaria, had shared their syringes with other known, infected cases. Helpern's most thorough investigation revealed a close association between the persons infected and the intimate sharing of syringes.

The incidence of malaria among addicts can be estimated only roughly from the various reports in the literature. R. H. Jaffé (16), in Chicago, reported forty drug addicts in a total of 112 cases of malaria. In 1934, 23 per cent of malaria patients admitted to the Cook County Hospital were addicts, in 1935, 36 per cent, and for the first half of 1936, 58 per cent. Helpern observed 49 cases in a six month period in New York City, and Bradley (12), 50 cases during an eleven month period in New Orleans. In 1938, 45 of 54 cases of malaria seen at Bellevue Hospital occurred in drug addicts (2).

The mortality from malaria in this group is high, ranging from 18 to 60 per cent. There was a mortality of 30 per cent among 86 cases of

falciparum-malaria which occurred at Bellevue Hospital from 1933 to 1938 (2).

Helpern performed 120 autopsies on drug addicts who died from malaria in New York City. The sizable mortality was due to the high incidence of falciparum infection in these patients.

Although the type of infecting parasite varies and mixed infections may be present, the outstanding species encountered in inoculation malaria is *Plasmodium falciparum* (aestivo-autumnal). In New York (8), there were found in 1934, 39 cases of the aestivo-autumnal, 1 case of tertian, and 9 of quartan malaria. In New Orleans (12), 37 of 48 cases were infected with the aestivo-autumnal variety, as were most of Biggam's cases. In a study of the morphology of the organism in some 200 cases, Most (2) found only one infection with *Plasmodium vivax*, one with *Plasmodium malariae* while all the others were caused by *Plasmodium falciparum*.

It is significant that the clinical manifestations of inoculation malaria in addicts in most cases are not suggestive of the clinical picture of malaria. Some of the diagnoses made before the presence of the parasites was disclosed were drug withdrawal, upper respiratory infection, toxic encephalitis, septicemia, tuberculous meningitis, and miliary tuberculosis. The majority of the non-comatose patients complained of chills, tremulousness, vague aches and pains, cough, headache, and feverishness. The majority attributed these complaints to drug withdrawal or adulterated drugs.

In Helpern's series (8, 13), the physical examination in the fatal cases revealed acutely ill patients with evidence of poor nutrition. The majority were comatose. In several instances, there was a fine purpuric rash on the lower extremities. Jaundice was noted in 12 per cent of the cases reported by Biggam (1) and occasionally in Helpern's series. A moderate to severe diarrhea, apparently due to intestinal localization, was common in those cases observed in Cairo. In most cases, there was evidence of previous intravenous injections, such as small, closely-placed, punctate, pigmented scars, thrombosed veins, and phlebitis. This is an important clinical finding which was present in both of our cases and which should be looked for carefully in all suspects.

The spleen was palpable in only 9 of 17 cases observed by Helpern. Malarial nephritis was noted by several observers. Fever was present in all cases at some time during the period of observation. According to Most (2), the temperature reaction in drug addicts with falciparum malaria is unpredictable. The temperature curve follows no given pattern. Any fever in a drug addict should be suspected of being malarial no matter how slight the fever or how irregular the course.

Laboratory examination usually revealed the parasites—rings or crescents. However, should malaria be suspected, repeated smears must be carefully searched to establish the diagnosis. In one instance (18), the

usual smears had been repeatedly negative, but because malaria was strongly suspected clinically, aspiration of the sternal marrow was performed, and this disclosed the presence of the parasites. In the case reported by Gardner and Dexter (21) of *quartan* malaria following a blood transfusion, careful search (including concentration of the blood and examination of the tibial marrow of the donor) did not reveal the parasite.

The localization of the parasite has been a striking feature in this group. In New York and New Orleans, the cerebral form was quite common, while in Cairo the intestinal localization was outstanding. One case reported by Biggam and Arafa (1) had been diagnosed by examination of scrapings of the mucous membrane obtained during a sigmoidoscopic examination.

The prompt institution of therapy in these cases is urgent. The mortality of the comatose, cerebral type is high despite all measures. Biggam and Arafa (1, 22) report on the use of plasmoquine and quinine sulfate with fair success. Quinine dihydrochloride (8, 23) intravenously and atabrine (14) have also been used successfully.

The significance of a clinical syndrome depends not only upon the frequency with which it is associated with a specific causative mechanism, but also upon the rarity with which its chief characteristics may be found in other conditions. The value of segregating the clinical manifestations is enhanced if it leads to rapidity of diagnosis and prompt institution of specific therapy. Although the incidence of drug addiction with malaria is not too common, the increase in the number of cases recognized since this association has been noted and looked for cannot be ignored. The presence of signs of venipuncture, thrombosed basilic veins, and irregular fever should lead one to suspect strongly narcotism and malaria.

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TRANSIENT VENTRICULAR FIBRILLATION

A STUDY OF THE FIBRILLARY PROCESS AND ITS DEVELOPMENT IN MAN

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"To sum up the evidence and write down briefly the nature of those disturbances, now included in the term ventricular fibrillation, is difficult because the condition remains undefined." —SIR THOMAS LEWIS.

Ventricular fibrillation is an alteration in the rhythm of the heart usually considered a terminal event in life; it is claimed that most sudden deaths are the result of its unexpected and abrupt onset in man (1 to 7). Although there are few records available of the cardiac mechanism during sudden death (8, 9), those that have been obtained in the course of the gradually dying human heart have revealed ventricular standstill to be present as frequently as ventricular fibrillation (10 to 20).

Ventricular fibrillation, however, is of extreme clinical importance because it may appear in man in a recurrent, transient and paroxysmal form associated with ineffective contractions of the ventricles resulting in attacks of syncope with epileptiform convulsions, the so-called Adams-Stokes seizures.

This study is based on observations of several hundred syncopal attacks recorded in eight patients, in whom electrocardiograms obtained prior, during and subsequent to the syncopal seizures invariably revealed the cardiac mechanism responsible for the attacks to be transient ventricular fibrillation. Since several patients experienced these seizures for periods varying from 9 months to $4\frac{1}{2}$ years, the question arises whether the change in the rhythm of the heart recorded during such attacks is identical to that observed in the experimental animal in which the arrhythmia has been well studied.

Historical review. That the human ventricles may develop transient fibrillation was first pointed out by Hering (21) and confirmed a year later by Deneke and Adams (22). Hering revived the heart of an adult eleven hours after death by forcing Ringer solution through its coronary vessels. Movements of the reactivated ventricles recorded kymographically revealed ventricular fibrillation on two separate occasions. The first lasted one minute and was caused by some mechanical stimulus. The second period lasted twelve minutes and followed the injection into the aorta of 12 cc. of calcium chloride solution.

In the extirpated heart of a decapitated woman, Deneke and Adams injected an equal volume of blood and Ringer solution at a temperature of 35 degrees and noted a transient period of ventricular fibrillation one half hour after death as well as ten hours later when sinus rhythm had been reestablished. They were the first to suggest that such alterations in the rhythm of the heart might result in "Adams-Stokes seizures" during life.

The first example of cardiac recovery from ventricular fibrillation in humans was recorded by Robinson and Bredeck (23) although in 1915 Hoffman (24) had obtained a graph in which a fibrillary period was evident but of too short a duration to give significant clinical manifestations. Since then there have been 36 patients with similar alterations in the cardiac mechanism reported in the literature. But the earliest electrocardiograms of ventricular fibrillation were obtained from a dog by Kahn, in 1909 (25). Levy and Lewis (26), however, first recorded the successive changes in the heart rhythms leading to ventricular fibrillation when they studied the combined effects of chloroform inhalations followed by the intravenous injection of small doses of adrenalin chloride in cats. They observed at first multiple premature beats of a particular form, which increased in number and eventually formed groups. These preceded at times a unidirectional, a bidirectional, or a polytopic type of ventricular tachycardia that suddenly changed to ventricular fibrillation with a rate of 400 to 800 oscillations of the galvanometer string per minute. The electrocardiographic waves were almost but not quite regular in incidence. With slower frequencies the individual undulations were irregular. They also noted a degree of waxing and waning in the excursions of the oscillations, a variability in their frequencies and occasionally weak string movements as a result of "tone" changes in the heart muscle. Similar appearances were seen after experimental obstruction of the coronary arteries (27) and also when fibrillation was induced by faradic stimulation or by poisoning with digitalis. By whichever of these means fibrillation was induced, it was preceded by variable tachycardias of ventricular origin.

Later Rothberger and Winterberg (28) registered electrical variations from points on the fibrillating ventricles of cats and dogs and, comparing these with complexes of the electrocardiograms obtained simultaneously, found these to be occasionally regular and synchronous.

On the other hand, Kisch (29) in similar experiments noted a marked asynchronism between the frequency of the oscillations in the electrocardiogram as compared with the partial electrogram. The complexes were identical with each other in form, shape and size. *However, the irregularity of the individual oscillations was the most common finding; the regularity, the rarest.* A greater frequency of the oscillations was noted towards the end of the fibrillary period rather than at the beginning. In some records they obtained alternations of the ventricular deflections.

Recently Wiggers (30) recorded in dogs similar punctate unipolar leads

simultaneously from three or four regions of the ventricles together with a standard electrocardiogram. Analysis of his records revealed a lack of incidence as well as differences in direction, form and amplitude of the most nearly corresponding waves. The tempo and regularity of the major deflections were also variable.

Wiggers (31) also compared the electrocardiograms and the intraventricular pressure curves of the natural fibrillary process of the ventricles in the exposed dog's heart following electrical shock with the actual movements of the ventricles shown in cinematographic records. For descriptive purposes he divided the course of this type of ventricular fibrillation into four stages. An (a) initial *undulatory* stage lasting only one or two seconds which consists of deflections in the electrocardiograms occupying an interval of 0.08 seconds or more. This process passes abruptly into (b) a *convulsive form of incoordination* when the initial rate is continued to one averaging 600 to 750 oscillations per minute and lasts from 15 to 40 seconds. As the frequency is now increased the contractions become less regular and the oscillations of the galvanometer string are rather violent and large. Occasionally the electrocardiographic deflections of this stage become even more rapid, attaining a frequency of 1560 per minute when they may pass to a (c) stage of *tremulous incoordination* which continues for two or three minutes. Now the electrocardiographic deflections increase in frequency to a rate varying between 600 and 1800 per minute and diminish in amplitude. Finally this stage of rapid incoordinate contractions is gradually replaced by a (d) stage of *progressive atonic incoordination* in which the visible waves become coarse and slower and in which the rate of propagation slows materially. Their frequency ranges from 540 to 720. The amplitude of the electrocardiographic deflections decreases continually until only small oscillations remain visible before there is a total cessation of electrical activity.

THE PRE-FIBRILLATORY PROCESS IN MAN

The acceleration of the basic ventricular rate. The development of transient ventricular fibrillation in man is dependent upon numerous coefficients, one of which is an acceleration of the basic ventricular rate in the presence of some form of auriculo-ventricular dissociation. The factors responsible for this acceleration are inherent in the ventricles and partly very likely the result of an imbalance in the extrinsic nervous mechanism of the heart.

In patients with normal sinus rhythm the ventricles may be accelerated through (a) a simple shortening of the sphygmie interval; (b) the onset of para-arrhythmias in which the heart rate is hastened by several interfering impulses that vie with each other for predominance as the pace maker, and; (c) the addition to the already increased ventricular rate of premature ventricular beats (32).

In patients who exhibit transient seizures of ventricular fibrillation in the course of transient auriculo-ventricular dissociation, the sinus rate may at first be halved by the appearance of blocked auricular beats (33). There follows then for a variable period an acceleration of the independently beating ventricles after the establishment of complete auriculo-ventricular dissociation. A further increase ensues through a series of alterations in the rhythm of the heart that have been observed also in patients with established heart block. (a) A basic idioventricular rate may be accelerated from an average of 17 beats per minute to one of 45 beats through a simple shortening of the sphygmic interval. At such times the impulse building center for the ventricles is somewhere in the auriculo-ventricular node, for all the complexes are as a rule supraventricular in form and resemble the basic deflections of the ventricles present during a normal sinus mechanism. (b) An acceleration of the ventricles may also take place through a step-like progression in which a slower idioventricular rate during total auriculo-ventricular dissociation alternates with a more rapid rate of the ventricles. In these records an impulse from the sinus pace maker yields periodically a ventricular response presenting a phenomenon of "dissociation with interference". The phase of supraventricular responses is at such times under the influence of the vagus nerves for compression of the carotid sinus causes the more rapid beating ventricles to slow. Premature beats of the ventricles, which are the immediate forerunner of transient ventricular fibrillation in such patients, appear after the basic ventricular rate has been raised to as high as 62.5 beats per minute (34). (c) The impulses for ventricular contraction during auriculo-ventricular dissociation may arise in the auriculo-ventricular node when the complexes are supraventricular in form, or they may originate in the upper part of one of the bundles when the complexes assume an aberrant form and are widened, notched and splintered. The impulses arising from one bundle may be at times faster than the other. Alternations of slower and faster rates in which dextrocardiograms alternate with levocardiograms have also been noted as precursory mechanisms of transient ventricular fibrillation. (d) Experimental studies have disclosed that a well timed extra stimulus to the heart can accelerate the ventricles abruptly. A similar mechanism has been observed to precede transient ventricular fibrillation. An interpolated extrasystole, well timed, has been found to accelerate a previously slow ventricular rate during established auriculo-ventricular dissociation from an average of 40 beats per minute to as high as 120 beats. The ventricular complexes of the electrocardiogram were different in shape, size and form before and after the extrasystole (35). (e) Occasionally ectopic foci in the ventricles have yielded runs of extrasystolic ventricular tachycardias that suddenly disrupted the slow ventricular rate and finally after a short period of heart rest, the cardiac mechanism reverted to one of auriculo-ventricular dissociation with alternate premature beats of the ventricles, an arrhythmia that

invariably preceded transient ventricular fibrillation. (f) Finally the heart rate during established auriculo-ventricular dissociation may be augmented by the interposition of premature beats of the ventricles at first appearing singly and occasionally in groups of two or three at the most before ventricular fibrillation sets in.

It would appear that these preliminary disturbances which may last from a few minutes to several days at a time facilitate the onset of transient ventricular fibrillation in man. There is experimental evidence that the ventricles are able to assume a higher rate of beating more readily if this rate is approached gradually than if it is approached abruptly. Mines (36) has pointed out that with increasing frequency of stimulation each wave of excitation in the heart muscle is propagated more slowly but lasts a shorter time at any one point in the muscle. The wave of excitation becomes slower and shorter. It follows that by gradual acceleration, the ventricles can be caused to beat at a higher rate than if the rate of stimulation is raised abruptly.

The "initial" premature beat of the ventricles. No matter what the underlying cardiac mechanism may be, whether normal sinus rhythm, transient heart block or established auriculo-ventricular dissociation, transient ventricular fibrillation is *invariably* preceded by the presence of premature beats of the ventricles. The intimate physico-chemical factors responsible for the appearance of such premature beats is still unknown. There may be some relationship between their development and advanced disease of the coronary vessels since a lack of blood supply has been found to enhance the irritability of the myocardium (37). Necropsy findings in two of our patients with transient ventricular fibrillation revealed marked arteriosclerosis and calcification with occlusions of the lumina of the vessels but no frank thrombosis or infarction of the heart.

These "initial" premature beats of the ventricles may form a bigeminal rhythm with the basic complexes for seconds, minutes or hours at a time before there is added to them the first of the disturbances that may be considered as fibrillation of the ventricles. Whether appearing singly or in groups with additional oscillations, these premature beats are at a relatively fixed distance from the basic complexes which form the dominant rhythm of the heart. For example, the distance between R_1 , R_2 , R_3 and R_4 and the succeeding premature beats of the ventricles in figure 1A are all equal to each other. Again the amplitude, duration and form of these "initial" premature beats may resemble each other from moment to moment. They may be either in the same direction as the basic complexes or opposite to them. (In fig. 1A the "initial" premature beats (E) are in the same direction as the basic complexes. In fig. 1B, they are opposite in direction.) The similarity of these initial beats in any one record preceding a transient seizure of ventricular fibrillation is an index that a constant and definite focus in the ventricles originates the stimulus for their produc-

tion. In the development of experimental ventricular fibrillation following electrical shocks, it appears important to stimulate repeatedly a definite "spot" in relation to anatomical landmarks. According to Wiggers the possibility looms large that the route of spread of the "initial" premature beat over muscle bundles is a factor in the induction of fibrillation.

•*The initial fibrillary periods of the ventricles.* The perpetuation of the transient fibrillary process in man seems to be conditioned by the recurrent development of short periods of fibrillation that may progressively increase in duration before longer periods appear. *Such a mechanism is unique for the human heart and has never been observed or produced in the experimental*

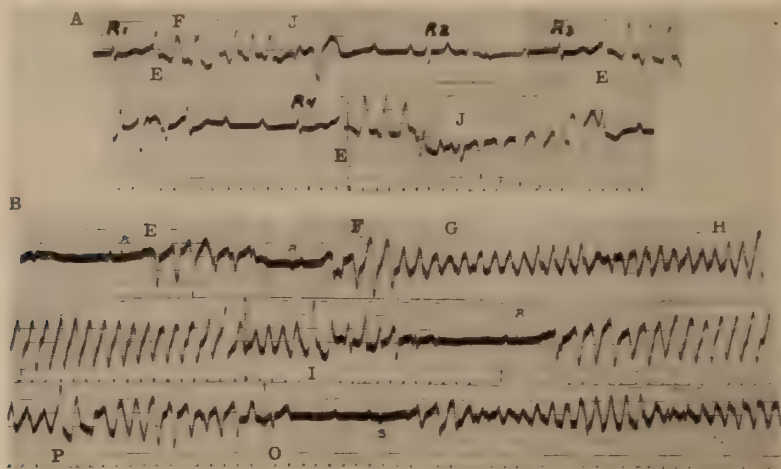


FIG. 1 (A) The pre-fibrillatory mechanism. Complete A-V dissociation. "Initial" premature beats (E) alternate with basic complexes (R_1 , R_2 , R_3 , R_4) from which they are equidistant and in the same direction. The ventricular oscillations which follow the "initial" premature beat may be disrupted by oppositely directed deflections (J).

(B) The "initial" fibrillary periods of the ventricles may vary from a few oscillations to thirty. The "initial" premature beat (E) may be opposite in direction to the basic complex. Beat by beat the succeeding oscillations diminish in amplitude (F-G). Later they may increase again (H) and be interrupted by a single premature beat of the ventricles (O) or a succession of these (I) before the basic rhythm is restored.

animal. At first there is added to the "initial" premature beat of the ventricles, a single widely aberrant ventricular complex usually lower in amplitude but at times larger (fig. 1A: F, fig. 1B: F). It resembles the series of oscillations that may follow it and constitutes the "initial" phases of fibrillation. These periods vary in duration from two to twenty complexes and as they increase progressively in number they herald a major seizure of ventricular fibrillation.

Beat by beat they may diminish in amplitude even after a few oscillations (fig. 1B: G) and remaining a fairly uniform size, progressively increase in amplitude again (fig. 1B: H) to be finally interrupted by a series of ven-

tricular deflections that are different in size, shape or form from any of the preceding ones (fig. 1B: I). At times these later deflections are all in the same direction but frequently they may be downwardly directed (fig. 1A: J). These oppositely directed deflections may also increase in their duration. For example, the undulatory phase in figure 1A following R_1 is interrupted by two such ventricular complexes directed downwardly, at R_3 by three and at R_4 by eight. Each one of these short fibrillary periods may be terminated finally by an isolated deflection which is different from all others and is followed by a pause (fig. 1B: O). This is very likely a premature beat of the ventricle. Frequently a series of such premature beats terminates the short period of fibrillation (fig. 1B: P).

These "initial" fibrillary periods, so-called because they invariably precede the longer seizures of transient ventricular fibrillation may recur anywhere from a few minutes to days at a time before the longer seizures appear. Again when the heart rests after recovery from a long seizure they may disappear completely.

THE FIBRILLARY PROCESS IN MAN

The shape, size and form, the frequency, duration and amplitude of the transient fibrillary process in man is unpredictable from moment to moment. In the same individual the oscillations may differ from record to record and from day to day. (Compare figs. 3, 4, 5, all obtained on the same patient.)

(A) At times after an initial period of large undulatory waves lasting from a few to several seconds and diminishing in amplitude, (fig. 3A), the ventricular oscillations may become uniform in character, rising and falling equally to a fixed base line. In such records they measure 8 to 10 mm. in height and averaging 280 to 300 deflections per minute (fig. 2A), they may persist for several minutes at one time. Abruptly they may decrease in height and frequency and be converted to an incoordinated type of mechanism (fig. 2B) averaging 240 to 360 oscillations per minute. A return to the more regular sequence of events may follow again (fig. 2C', D), before there is finally a change to the basic mechanism of the heart. It is such records that may be likened to the flutter waves observed in the auricles and because of their regularity be termed *ventricular flutter*.

Ventricular flutter waves may be wider (0.36 seconds each) and slower in frequency (130 to 170 oscillations per minute) (fig. 3D, E). I have also observed ventricular flutter when as a result of asphyxial effects their rate was only 90 oscillations per minute. The transitions from ventricular flutter to ventricular fibrillation and vice versa are very abrupt and often when flutter appears towards the end of a fibrillary period it may change suddenly to an ectopic ventricular tachycardia that presages the return to the basic heart mechanism and the termination of the attack (fig. 3E).

(B) In fully developed transient seizures of fibrillation the amplitude

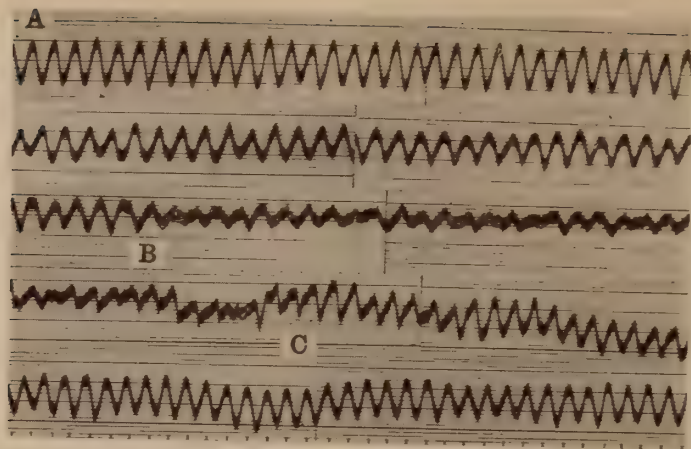


FIG. 2. Transient ventricular flutter. (A) Uniform oscillations 8-10 mm. in height with a frequency of 280-300 abruptly change to a lower amplitude averaging 240-360 oscillations per minute (B) and return to ventricular flutter with a more rapid rate (C).

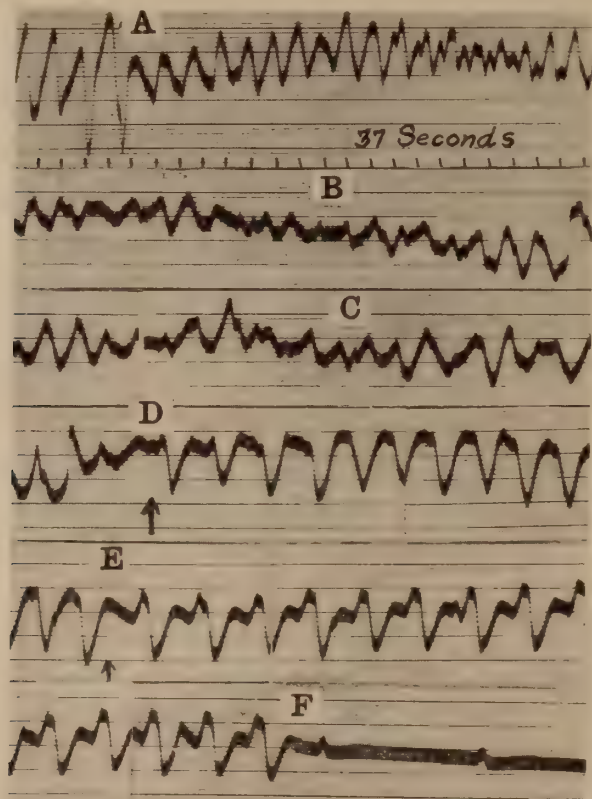


FIG. 3. Transient ventricular flutter, fibrillation and tachycardia. (A) The undulatory phase following immediately the "initial" premature beat consists of large oscillations measuring 0.04 second in width and 25 mm. in height. (B) Abruptly they may diminish in amplitude and at first increase in frequency and then slow again. (C) This irregular mechanism may continue for a little over one minute and change to ventricular flutter (D) with a frequency of 130-170 oscillations. A ventricular tachycardia (E, F) may be the final mechanism before the heart reverts back to its basic mechanism.

and frequency of the deflections are influenced by repeated seizures which result in profound asphyxial states so that the height of the complexes may

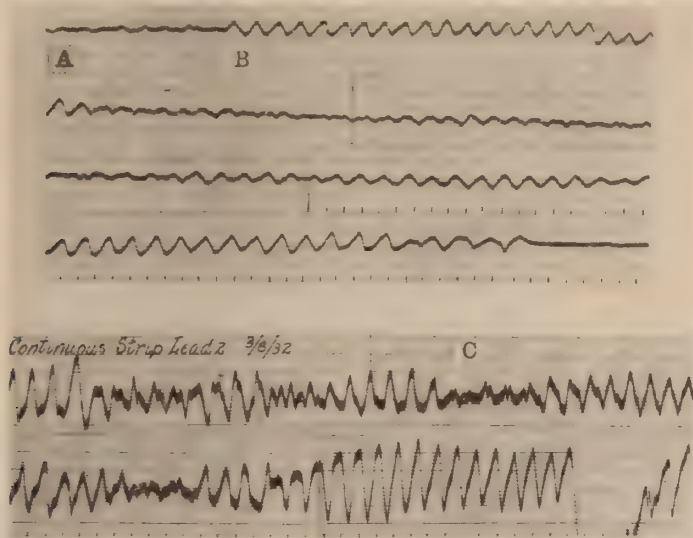


FIG. 4. Impure ventricular flutter. (A) At times the amplitude of the ventricular oscillations measures only 1-2 mm. Such deflections may alternate with regular ones averaging 200-220 per minute. (B) This resembles the mechanism of impure flutter found in the auricles. (C) In the same patient the ventricular oscillations during transient ventricular fibrillation may differ in size, shape, form, amplitude and duration from time to time.

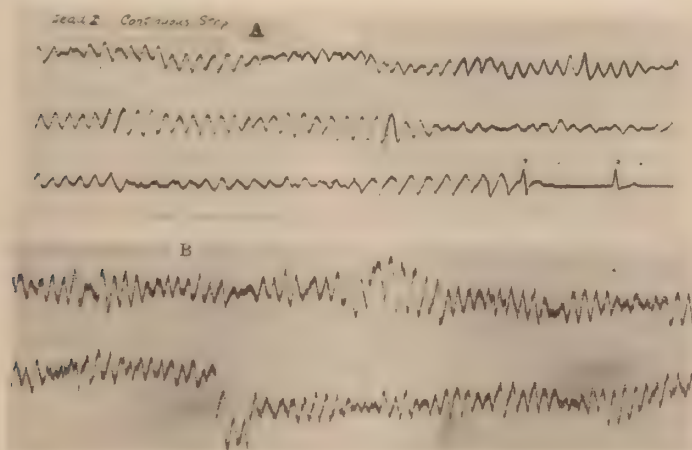


FIG. 5. Transient ventricular fibrillation. (A) The oscillations are of a frequency averaging 360 per minute and are rounder in contour than the peaked type seen on another occasion (B) when they averaged 380-420 per minute.

be only one or two millimeters (fig. 4A), and the waves are hardly discernible. Such periods in which the frequency of the records cannot be

determined accurately may alternate with a more regular type oscillation (fig. 4B) averaging 200 to 220 per minute which closely resemble ventricular flutter. Such records may be likened to the mechanisms observed in the "impure flutter" of the auricles. That this need not be considered a terminal event may be gained from other records obtained on such a patient six months later (fig. 4C).

A further effect of the asphyxial state is to diminish the ventricular oscillations in height so that the electrocardiograms almost resemble a straight line (47). It is very likely that the contractility of the heart also suffers for with the restoration of the basic heart rhythm after such an episode, the apical heart sounds are barely audible. On the other hand, the heart sounds are audible and normal in pitch on other occasions after the revival of the heart, when the preceding oscillations of the fibrillary period are large and well delineated.

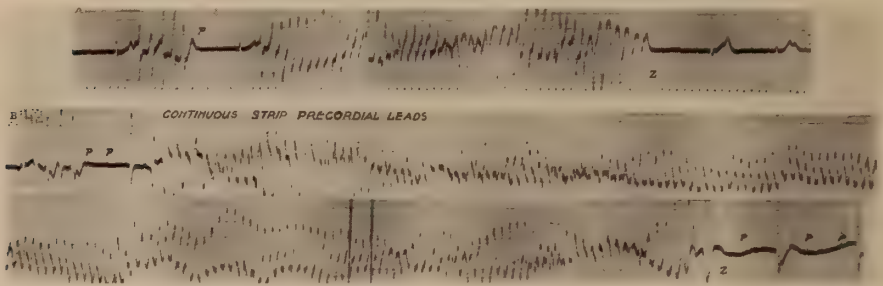


FIG. 6. Transient ventricular fibrillation. Records obtained with precordial leads to magnify the fibrillary waves. (A) The ventricular oscillations are variable from moment to moment. There is a waxing and waning of the amplitude and the frequency averages 300. No T waves are visible. The auricles are not interfered with but their rate is slowed after a longer seizure. (B) The post-undulatory pause (Fig. A, B-Z) is variable. It measures 0.4 second in A and 0.8 second in B.

(C) The rate of the oscillations in transient ventricular fibrillation may vary from 130 in the more regular sequence of events to an average of 460 (fig. 4C) in the more irregular patterns. The slowest oscillations of transient ventricular fibrillation are invariably observed in records obtained pre-terminally so that frequently only 20 to 30 large, broad and ill-defined markedly aberrant complexes per minute may be the only evidence that there is still some electrical action in the ventricular musculature.

(D) Periodic alterations in the height and width of the fibrillary waves resembling the waxing and waning of the graphs obtained during Cheyne-Stokes respirations have been noted infrequently independent of the type of respiration present (fig. 4C). These may be best seen in electrocardiograms obtained with precordial electrodes placed directly over the region of the ventricles so as to magnify the oscillations (fig. 6).

(E) The longest period of transient ventricular fibrillation recorded was

slightly over six minutes and as many as 300 attacks lasting from fifty seconds to three minutes each were recorded in one patient during twenty-four hours. Two patients are known to have lived four and one-half years each during which time they experienced numerous seizures of transient ventricular fibrillation finally dying in one of these attacks.

(F) The fibrillary process in man may be ended by either a single premature beat of the ventricle or the last of a series of grouped extrasystoles sometimes resembling each other and at other times appearing as if they had their origin in different foci. Invariably, however, the end of fibrillation in man is terminated by a post-undulatory pause.

THE POST-UNDULATORY PAUSE

The short diastolic period which ends the fibrillatory process of the heart and is followed by the re-establishment of either rhythmic or coordinated heart beats or an intermediary idioventricular rhythm has been termed by Gewin (38) the post-undulatory pause. Similar pauses ending fibrillation were observed by Hoffa and Ludwig (39) following faradization of the ventricles. Vulpian (40) attributed this pause to a vagal influence, now known to be negligible, but Fonrobert (41) felt that the heart was so fatigued that it needed a long rest period before it resumed its normal contractions. Winterberg (42) faradized the ventricles and concluded from kymographic tracings that the post-undulatory pause was dependent upon the frequency of ventricular "contractions" preceding it and independent of the strength of electrical current used in stimulation. He noted that after prolonged ventricular fibrillation the post-undulatory pause was also prolonged and that the physiological period during which impulse formation takes place was frequently disturbed by ventricular fibrillation. Consequently the post-undulatory pause of the ventricles was usually not compensatory like the post extrasystolic pause. Winterberg also felt that the duration of the post-undulatory pause was dependent upon the time of the appearance of the first auricular systole after the cessation of the fibrillatory process.

De Boer's (43) electrograms of the frog's heart, reveal that under similar conditions of electrical stimulation and intensity of stimulus, the duration of the post-undulatory pause is variable from time to time, at times being longer and at times shorter than the duration of a true intersystolic interval when the basic rhythm has its origin in the sinus node. During ventricular fibrillation the excitation wave presumably circles the ventricles and the fibrillatory process ceases as soon as the wave strikes refractory tissue. The duration of the post-undulatory pause would then be dependent upon the exact period of the heart in which fibrillation ceases and upon the "metabolic" state of the ventricular musculature present at that particular moment. If the fibrillatory process stops very shortly before a sinus impulse reaches the ventricles when these are still in a refractory state,

another sinus period would have to elapse before a normal ventricular contraction could take place. Consequently between the long and short post-undulatory pauses may be found all forms of intermediary variations depending upon the exact moment when fibrillation ceases and upon the state of the refractoriness of the ventricles. Again very frequently the shorter periods of ventricular fibrillation may be ended by single or multiple premature beats of the ventricles and obviously the pause which follows these will be variable, depending upon the antecedent cardiac rhythm.

These conclusions find ample confirmation in the electrocardiograms of patients whose basic rhythm originates in the sinus node. In patients whose basic rhythm is that of auriculo-ventricular dissociation, the duration of the post-undulatory pause is definitely related to the duration of the antecedent period of ventricular fibrillation. It bears no relationship to any extrinsic nervous influence, for the phenomenon can occur in the atropinized patient as well as in the heart accelerated by epinephrine. It is very obvious that when the duration of transient periods of ventricular fibrillation are longer, the heart suffers from asphyxia. Since the asphyxial effects upon the auricles and ventricles tend to increase the sphygmie intervals between them it follows that the post-undulatory pause will be greater when the antecedent period of asphyxia has been longer. The appearance of the first auricular systole after the cessation of ventricular fibrillation will likewise be longer.

If auricular standstill should follow fibrillation of the ventricles for any length of time, then the duration of the post-undulatory pause would be as long as the interval between the last of the fibrillary waves and the first beat of the intermediary idioventricular rhythm.

A slight elevation of the electrical string seen occasionally after the last of the fibrillary waves in the frog's heart and considered by De Boer (44) to be a retrograde auricular beat is in reality a "u" wave, since the shape, size and form of these elevations even when magnified (with chest leads) is totally different from the auricular complexes observed after this elevation.

THE INFLUENCE OF VENTRICULAR FIBRILLATION ON THE AURICLES

Ventricular fibrillation induced in the bled frog's heart by an electric stimulus reveals that during fibrillation of the ventricles, the auricles continue their pulsations regularly (45). In the longer runs the auricles display some electrical anomalies caused no doubt by intercurrent retrograde excitations running from the ventricles to the auricles.

In ventricular fibrillation caused by electric shock in the dog's heart, the auricles maintain a variable rhythm for a length of time. Sometimes their contractions terminate before ventricular fibrillation ceases and at other times they outlast fibrillation. With progressive phases of asphyxia, the

auricular rate soon decreases and the contractions first increase but soon decrease in vigor. Frequently heart block develops between the right and left auricles and on several occasions independent rhythms have been observed, suggesting that a rhythmic center becomes active in the left auricle.

On the other hand, fibrillation produced by perfusion in the ventricles of the dog has no distinct influence upon the auricles. The auricles continue to beat regularly but the energy of their pulsations decrease rapidly and they become imperceptible within one or two minutes. After this transitory pause they assume their original beating. This phenomenon according to Frederique (46) is undoubtedly due to momentary excitation of the inhibitory mechanism. Sections of the bundle of His do not modify this change in rhythm. The weakness of the auricular pulsations, that is, in the contractility of the auricles, is due to a diminution in the coronary flow and is not the direct result of ventricular fibrillation.

In human electrocardiograms short runs of ventricular fibrillation do not interfere with the auricular contractions. The auricular complexes may be easily recognized superimposed upon the ventricular deflections which they distort but slightly. However, in periods of ventricular fibrillation lasting more than 10 seconds the auricular complexes cannot be discerned in the electrocardiogram until cessation of the fibrillary process. After the revival of the heart both the rate and rhythm of the auricles will depend upon the duration of the antecedent period of ventricular fibrillation. Longer periods of ventricular fibrillation result in longer periods of asphyxial states and these in turn influence the rate and rhythm of the auricles best seen when fibrillation ceases. At first the auricular rate will be slow and irregular and then the auricles may accelerate above the basic heart rate during the so-called intermediary idioventricular rate and rhythm of the heart (47). Eventually transient periods of auricular fibrillation and auricular flutter may supervene. These may last as long as 122 hours. Such abnormal auricular states have never been seen to occur immediately after the cessation of ventricular fibrillation but invariably some time after the revival of the heart.

SUMMARY AND CONCLUSIONS

1) An electrocardiographic study was made of the fibrillary process and its mode of development in eight patients who experienced such seizures. These records were compared with those obtained from animals (frogs, rats, dogs, cats and sheep) following faradization of the ventricles, poisoning with drugs or after ligation of the coronary arteries.

2) The preliminary alterations in the rhythm of the heart that lead to transient ventricular fibrillation consist of (a) an acceleration of the basic ventricular rate during the presence of some form of auriculo-ventricular dissociation; (b) the onset of "initial" premature beats arising from a con-

stant focus in the ventricles as judged by their persistent similarity; and, (c) the development of short runs of irregular ventricular oscillations which increase progressively in duration and recur from moment to moment.

3) It appears that these short recurring periods of ventricular irregularities are the "initial" fibrillary periods of the ventricles. They are a distinct and unique feature in man and have not been noted in animals. They invariably foreshadow the appearance of longer seizures.

4) The "initial" premature beats of the ventricles are associated clinically with an effective ventricular contraction which is audible at the apical region of the heart.

5) The "initial" fibrillary periods are associated clinically with progressive diminishing heart sounds for the first 2 or 3 oscillations. The heart sounds disappear entirely after the fourth oscillation and because of the diminished blood supply to the brain, consciousness is lost if they last 20 to 40 seconds. A typical Adams-Stokes seizure with epileptiform convulsions, apnoea and incontinence of feces and of urine supervenes if these oscillations last longer than 40 seconds.

6) The ventricular oscillations that yield these Adams-Stokes seizures are of two distinct types. One type of deflection is uniform in character, rising and falling evenly to a base line with an amplitude of 8 to 10 mms. and a frequency of 130 to 300 oscillations per minute.

With progressive asphyxia of the heart, the rate may be lowered to 90 per minute. The QRS complexes are continuous with each other so that the T waves are totally absent. This mechanism may be considered as one of *ventricular flutter*.

7) The second type consists of irregular oscillations averaging 130 to 460 per minute and varying in amplitude from 3 to 18 mm. in height. They differ in shape, size and form as well as frequency, duration and amplitude from record to record and moment to moment. Periodic waxing and waning of the height of the oscillations may be present and occasionally alternation of the ventricular complexes may be seen. They may persist as long as 6 minutes at one time and as many as 300 periods have been recorded in one patient during 24 hours.

8) Transient ventricular flutter and fibrillation may be ended by a single premature beat of the ventricles, a succession of these, or a run of ventricular tachycardia. A post-undulatory pause, however, invariably precedes recovery.

9) The auricles maintain their regular rate and rhythm during ventricular fibrillation except in the longer periods when they may be slowed with an irregular rate and at times stand still because of asphyxia.

10) Except for the frequency and duration and its unusual transient, recurrent and reversible nature associated with profound clinical disturbances, the fibrillary process in man is identical with that in animals.

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THROMBO-ANGIITIS OBLITERANS AND POLYCYTHEMIA VERA

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When a patient who has presented signs of thrombo-angiitis obliterans subsequently develops polycythemia vera, the suspicion arises that the peripheral thromboses at the onset were really due to the latter disease, and that the diagnosis of thrombo-angiitis obliterans was incorrect. The following cases are presented because of their relation to this problem.

CASE REPORTS

Case 1. History (Adm. 449732). J. B., a salesman, was in good health up to the age of 36 years. At that time he began to complain of intermittent claudication in the left calf after walking three to four blocks. Nine months later in June 1935, he had an acute coronary occlusion and was confined to bed for six weeks. He was first seen in the Peripheral Vascular Clinic in September, 1935. He gave a history of having smoked 30 cigarettes daily, but he had stopped smoking after the coronary attack. The patient was a healthy looking, well nourished young man. Examination showed a normal circulation in the upper extremities. In the right leg the posterior tibial artery was open, the anterior tibial and dorsalis pedis were closed. In the left leg the posterior tibial artery was closed, the anterior tibial and dorsalis pedis were open. Oscillometer readings (Table 1) were moderately reduced. The blood Wassermann reaction and urine examinations were negative. The blood volume was 65 cc. per kg. The blood pressure was normal (Table 2). X-ray examination of the chest showed no enlargement of the heart. The electrocardiogram showed evidence of myocardial damage due to recent coronary occlusion. The pulse was regular. A diagnosis of thrombo-angiitis obliterans complicated by coronary occlusion was made. Since the symptoms were mild, no treatment was recommended. The patient was told to refrain from the use of tobacco and to return for re-examination every three months. In addition, he was to be observed frequently in the cardiac clinic.

He followed this advice and for a time all went well. The circulation in his legs gradually improved as reflected by relief of symptoms and increase in the oscillometer readings (Table 1). He was able to walk without pain. His cardiac condition likewise gave him no trouble. He returned to work.

In March, 1937 he returned to the clinic complaining of pain in the right second toe and an abrupt drop in his oscillometer readings was noted. He continued to have pain in the right foot throughout the summer and when examined in October, he admitted that he had resumed smoking. He was warned of the danger, and for a number of months again stopped the use of tobacco. His circulation again improved. In the Spring of 1938 he returned with an ulcer on the right fifth toe. At this time small intravenous injections of 5 per cent saline solution were administered twice a week and later once a week. The amount given did not exceed 175 cc. at each injection because of the coronary disease. The toe healed in five weeks, and he appeared

to be doing well. On subsequent examinations further marked reductions in oscillometer readings and complete disappearance of the pulses in both feet were noted. Again the patient admitted that he had resumed smoking. In December, 1939 he developed a painful ulcer on the right first toe, and for this reason he was admitted to the hospital. In brief summary, then, the course of this patient's illness was char-

TABLE 1
Oscillometer readings in case 1

DATE	LEFT ANKLE	RIGHT ANKLE	
September 1935.....	1.0	1.5	
December 1935.....	1.5	2.0	
March 1936.....	1.5	2.0	Stopped smoking
June 1936.....	2.5	3.0	
September 1936.....	2.5	3.5	
March 1937.....	1.25	1.5	
July 1937.....	1.5	1.0	Resumed smoking
October 1937.....	1.25	1.0	
February 1938.....	2.0	1.25	Stopped smoking
June 1938.....	2.0	1.5	
August 1939.....	1.75	0.25	Resumed smoking
December 1939.....	1.5	0	

TABLE 2
Blood pressure readings in case 1

DATE	SYSTOLIC	DIASTOLIC
September 1935.....	142	90
November 1935.....	140	92
April 1936.....	124	82
May 1937.....	132	90
June 1937.....	160	110
July 1937.....	175	100
June 1938.....	176	120
August 1938.....	182	110
April 1939.....	170	115
December 1939.....	204	120
January 1940.....	198	120
February 1940.....	210	100

acteristic of individuals with thrombo-angiitis obliterans, who improve when they stop smoking, and regress when they resume the use of tobacco.

While the above events were taking place, other changes were noted. These were a gradual rise of blood pressure (Table 2), gradual enlargement of the heart as seen on x-ray examination of the chest, and the development of some signs of mild cardiac failure, such as dyspnea, cough, and edema of the legs. Digitalis was given and these symptoms improved. Numerous examinations made in the cardiac clinic during

the years 1935 to 1939 showed no evidence of enlargement of the liver or spleen. A blood count in June 1937 showed hemoglobin 112 per cent, red blood cells 6,390,000, white blood cells 13,600. Such a blood count is not unusual in thrombo-angiitis obliterans, and caused no comment at the time.

On admission to the Medical Service of Dr. B. S. Oppenheimer in December 1939, the patient presented the typical signs of a polycythemia vera. There was marked enlargement of both the liver and the spleen. The hemoglobin was 90 per cent, red blood cell count 8,660,000, white blood cell count 24,800, platelets 1,600,000, and blood volume 132 cc. per kg.¹ The heart was enlarged and the blood pressure was 204 systolic and 120 diastolic. During his hospital stay he had three attacks of frank ventricular failure requiring intensive therapy, including oxygen, digitalis, and diuretics. About one month after admission he showed signs of severe intestinal bleeding. He was treated with radiotherapy to the long bones. The ulceration of the toe responded favorably to conservative treatment. He was discharged two months after admission, greatly improved. He has continued in good condition up to the present.

Comment. When first seen this young man presented the typical features of thrombo-angiitis obliterans, the history of intermittent claudication, the use of tobacco, the signs of peripheral arterial occlusion in both legs, the reduced blood volume. There were no indications of polycythemia vera, no ruddy color, no enlargement of liver or spleen, no increase in blood volume. The progress of his peripheral vascular disease fluctuated with his use or disuse of tobacco, a characteristic feature of thrombo-angiitis obliterans.

There is no question that this patient subsequently showed all the classical signs of polycythemia vera. Could he have been suffering from this disease at the onset? Peripheral arterial thromboses are frequently seen in this condition. Is there a stage of polycythemia during which the spleen is not enlarged and the blood volume is not increased? If so, how is one to recognize the disease in this period?

Case 2. History (Adm. 464493). M. H., a man, 30 years of age was first seen in November, 1930. He gave a history of intermittent claudication in both legs, worse on the right, after walking four blocks. His symptoms had been present for 1½ years. He stated that he smoked about 40 cigarettes a day. Examination showed a well nourished young man. The heart was normal and blood pressure was 130 systolic and 80 diastolic. Palpation of the abdomen revealed no evidence of enlargement of the liver or spleen. Both popliteal arteries were pulsating. The left anterior tibial and dorsalis pedis arteries were likewise open. The left posterior tibial was closed and all pulses were closed in the right foot. The oscillometer readings were considerably reduced (Table 3). Blood Wassermann reaction, urine examination, and x-ray examinations of chest and legs showed no abnormalities. A diagnosis of thromboangiitis obliterans was made, smoking was prohibited, and the patient was treated with intravenous injections of hypertonic sodium chloride solution. He showed steady improvement as reflected both in relief of symptoms and improvement

¹ Almost all the blood counts and determinations of the blood volume reported in this paper were performed by Dr. Nathan Rosenthal or members of his department.

in oscillometer readings. Early in 1933 he was able to walk a mile without discomfort and treatment was, therefore, discontinued. This patient has never resumed smoking since he stopped in 1930. He has had no recurrence of symptoms in his legs up to the present time, and the circulation remains adequate. In October 1940 examination showed the left posterior tibial and dorsalis pedis pulses present. The right posterior tibial was also pulsating, the right anterior tibial and dorsalis pedis arteries were still closed. His oscillometer readings (Table 3) were much increased reflecting the greatly improved circulation in both legs.

In April 1932, because of the onset of abdominal pain after meals, he was referred to the gastro-intestinal clinic. Abdominal examination was negative at that time. A diagnosis of duodenal ulcer was made, and he was treated for this condition. In April 1934 it was first observed that he had developed a ruddy color. At this time he was studied in the Hematology Clinic. The blood examination showed, hemoglobin 126 per cent, red blood cells 8,130,000, white blood cells, 9,500, platelets 560,000, blood volume 139 cc. per kg. The spleen was not palpable. The diagnosis of polycythemia vera was made at this time.

This patient has been admitted to the Medical Service of Dr. George Baehr on four occasions, in 1934, 1936, 1937, and 1940, for treatment of recurrent abdominal symptoms due to his duodenal ulcer. He has continued to show the characteristic blood picture of polycythemia vera. On his last admission in May 1940, his blood

TABLE 3
Oscillometer readings in case 2

DATE	LEFT ANKLE	RIGHT ANKLE
November 1930.....	1.0	0.25
August 1931.....	1.5	1.00
October 1933	2.5	1.5
April 1936.....	2.5	1.5
October 1940.....	3.0	2.0

pressure was 116 systolic and 80 diastolic, hemoglobin 84 per cent, red blood cells 11,800,000, white blood cells 30,000, platelets 850,000, blood volumes 130 cc. per kg. Since 1934 his spleen and liver have been enlarged.

Comment. The diagnosis of thrombo-angiitis obliterans appears justified in this patient on the basis of his history of intermittent claudication beginning at the age of 28 years, the use of tobacco, and the evidence of occlusive peripheral vascular disease. Unfortunately no blood volume determination was made when he was first examined. His arterial disease gradually improved with cessation of smoking, and there has been no recurrence of symptoms in the seven years since treatment for the legs was discontinued. These are characteristic features of thrombo-angiitis obliterans.

It was not until four years after he was first seen that the characteristic signs of polycythemia, the ruddy color, the enlarged spleen, the increased blood volume, were first observed. These signs have persisted to the present time. His clinical course has been complicated by the presence of a duodenal ulcer.

Case 3. History (Adm. 297999). At the age of 23 this patient, L. B., developed pain and superficial phlebitis in the right foot. Three years later he began to complain of intermittent claudication in the left leg. When first seen at the Peripheral Vascular Clinic in December 1928 he was 31 years of age. He was a well nourished young man. Evidence of advanced impairment of circulation was noted in both lower extremities. The right femoral pulsation could be felt, the left was absent. Both popliteal arteries were closed, and there was no pulsation in either foot. His oscillometer readings were: left calf, faint; left ankle, 0; right calf, 1; right ankle, 0.5. The liver and spleen were enlarged. His hemoglobin was 132 per cent, red blood cells 6,860,000, blood volume 105 cc. per kg. The Wassermann reaction was negative. Urine examination showed three plus albumin, no sugar. He was advised to avoid the use of tobacco and he has followed this advice. Because of the albuminuria, saline injections were not given and his legs were treated with diathermy. He was referred to the Hematology Clinic for treatment of the polycythemia. He has been seen from time to time in the Clinic for Peripheral Vascular Disease. His legs have slowly improved and at no time have given him any serious trouble. He was last examined in October, 1940. He had been without treatment for either the polycythemia or the peripheral vascular disease for several years. He continued in excellent health and reported that he could walk indefinitely without pain. Examination showed the left femoral pulse still absent, and no pulsation in the left foot. The right femoral, popliteal, and dorsalis pedis pulses were now palpable, the right posterior tibial still closed. The oscillometer readings were: left calf, 1; left ankle, faint; right calf, 3; right ankle, 2.

Comment. The diagnosis of thrombo-angiitis obliterans in this case rests upon the presence of advanced peripheral vascular disease in a man in his twenties, and the characteristic improvement with cessation of smoking. It is unlikely that the arterial occlusion was due to polycythemia. The latter condition was at no time severe, and throughout the period of observation his platelet and white blood count have been normal. The diagnosis of polycythemia was made on the enlarged spleen, high red cell count, and moderately increased blood volume.

DISCUSSION

Unquestioned examples of the occurrence of thrombo-angiitis obliterans and polycythemia vera in the same patient are rare in medical literature. In 198 cases of polycythemia vera observed at the Mayo Clinic (1, 2) between 1912 and 1936, only one case is regarded as having had thrombo-angiitis obliterans. Since pathological examination of the amputated leg in this case showed the lesions of arteriosclerosis, the diagnosis of thrombo-angiitis obliterans is open to question. One case in a man 43 years old is reported by Weber, (3) but no blood volume studies or pathological data are given. One patient (Case 1) reported by Dameshek and Henstell (4) may be regarded as a true instance of this combination of diseases. Reznikoff (5) stated that in his clinic there was a frequent association between thrombo-angiitis obliterans and polycythemia vera, but does not substantiate his statement by citing a single case. It does not need to

be emphasized that all thrombotic arterial disease is not thrombo-angiitis obliterans (6).

The three cases reported in this paper are the only ones observed among approximately 100 cases of polycythemia vera admitted to The Mount Sinai Hospital in the past 20 years (7). On the other hand, the subsequent development of polycythemia vera in patients originally diagnosed as thrombo-angiitis obliterans is even more rare. In over 1300 cases of thrombo-angiitis obliterans observed by the writer (8), most of whom have been followed for many years, these are the only three patients who showed both diseases.

Taking into consideration the infrequency with which both diseases occur in the same patient, the rare association must be regarded as a coincidence. The suggestion made by Reznikoff that thrombo-angiitis obliterans might secondarily produce polycythemia vera through the development of vascular changes in the bone marrow is not supported by clinical experience. If this were true, the association of the two diseases would be much more frequent.

SUMMARY

1. Three cases are presented in which thrombo-angiitis obliterans and polycythemia vera occurred in association in the same patient.
2. This combination is extremely rare, and should be regarded as coincidental.

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THE BLOOD IODINE IN THE PERIOD AFTER THYROIDECTOMY

PRELIMINARY REPORT

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We have had experiences during the past two years with a method for the determination of the iodine level in the circulating blood which has proved satisfactory (1). The details of this method will be published elsewhere. It is sufficient to state that we are able to determine the blood iodine with an average error of about five per cent. We also have established that dialysis against running tap water entirely eliminates all ingested iodine which has been administered in the form of potassium iodide or Compound Solution of Iodine U. S. P. (Lugol's Solution) and leaves the normally occurring blood iodine intact. By our method the normal blood iodine does not exceed four gamma per hundred cubic centimeters of whole blood and there is no significant amount of iodine which is dialyzable (inorganic) if no iodine has been ingested. It is our opinion that the so-called "inorganic" fraction of the normal blood iodine is an artifact of chemical manipulation.

This study is an attempt to add to our knowledge of the events in the period immediately following thyroidectomy. Ever since the earliest attempts at the surgical treatment of Graves' disease, surgeons have encountered inexplicably severe postoperative reactions. This reaction is dramatically impressive and has been described in the literature as a "thyroid storm," "thyroid crisis" or "postoperative toxic reaction." In the era before the routine use of pre-operative iodine medication these unfortunate reactions were very frequent and in the hands of very competent surgeons it was not unusual to have mortalities varying between 10 and 20 per cent. Many of these deaths were due to thyroid crises which began within 24 hours after the operation and often ended fatally in another 24 or 48 hours. The typical history of a thyroid crisis is somewhat as follows. A patient is suffering from severe or moderately severe Graves' disease. The pre-operative course is not very satisfactory. The patient fails to gain weight, the tachycardia persists and the basal metabolic rate fails to decline during iodine medication. Often there is extreme motor and psychic unrest. Appetite is poor and sleeplessness is prominent. Frequently there is diarrhea or vomiting or both. Mild manic states may

supervene. With some uneasiness the surgeon decides to operate "to stop the progress of the disease" or he is induced to operate "as a life-saving procedure." The operation may be accomplished without incident or more frequently the tachycardia increases and the patient is returned to bed. Soon marked restlessness occurs and the tachycardia becomes even more marked. After 12 hours or so the temperature has begun to reach alarming heights and then severe hyperpyrexia (105° to 108°F.) appears. There is marked restlessness and frequently acute mania. The patient becomes incontinent and lapses into coma. The pulse rate may reach 200 per minute and the diastolic pressure approaches zero. Death occurs from 24 to 72 hours after the operation. The usual treatment is the use of sedatives and the administration of iodine by the intravenous route. All observers are agreed that the prognosis in a fully developed crisis is extremely grave and it is doubtful whether any therapy is of much value once the thyroid storm has really begun. The only therapy so far which seems to have been of service has been prophylactic. Operation should never be performed as an emergency procedure and should be done only when the patient's disease has been held in check by medical means and iodine. Most clinicians are aware of this now and the incidence of post-operative thyroid storms has diminished almost to the vanishing point in many clinics.

The nature of the thyroid storm. Because of the fact that these reactions usually followed operative procedures upon the thyroid gland it was generally believed that the crisis represented some acute augmentation of thyroid activity possibly as a result of mechanical expression of thyroid secretion into the circulation during operative manipulation or absorption from the wound bed. That such an inoculation of the blood stream may occur has been suggested by the recent studies of Lerman (2) who found a positive precipitin reaction for thyroglobulin in the blood from the thyroid vein only after trauma to the gland. On the other hand crises have occurred in patients with Graves' disease following operations far from the thyroid gland; such as pelvic operations, tonsillectomy or even the injection of varicose veins of the legs. In fact, not infrequently, we observe such thyroid storms while the patients are still on the medical wards being prepared for surgery. These "medical storms" are almost always ushered in by one of the acute upper respiratory infections to which these patients are so susceptible. Although the obvious stimulation that occurs during a crisis has led most observers to suspect an acute intoxication as the cause of the symptoms this view has not been the only one entertained. As early as 1925 Kessel and Hyman (3) recommended the intravenous use of thyroxine to combat the effects of the thyroid storm on the assumption that the sudden withdrawal of the thyroid secretion might lead to acute symptoms in patients previously established on a high level of hormone. In 1931 Bier and Roman (4) published a few cases in which they reported

that there was a postoperative drop in the blood iodine level and they attributed the postoperative reaction to this and called it "Hypothyrox-aemischer Shock." Gutzeit and Parade (5) obtained results in direct contradiction to those quoted above. The methods for the determination of iodine available to all these authors at those times must now be considered too inaccurate to warrant the conclusions drawn.

We are aware that the sudden withdrawal of the secretion of a hyper-functioning gland may lead to acute symptoms. The occurrence of tetany following the removal of a parathyroid adenoma and of acute adrenal insufficiency following removal of an adrenal cortical tumor are well known. However, in these instances the symptom complex produced is that which is well recognized as due to a deficiency of the particular gland studied. In

TABLE I
Summary of data (blood iodine values in gamma per cent)

CASE NUMBER	AGE	SEX	BASAL METABOLIC RATE ON ADMISSION	BASAL METABOLIC RATE BEFORE OPERATION	NUMBER OF DAYS ON IODINE MEDICATION	BLOOD IODINE ON ADMIS- SION	BLOOD IODINE AFTER IO- DINE MEDICATION (IMME- DIATELY PREOPERATIVE)	BLOOD IODINE IMME- DIATELY POSTOPERATIVE	BLOOD IODINE 4 HOURS POSTOPERATIVE	BLOOD IODINE 8 HOURS POSTOPERATIVE	BLOOD IODINE 24 HOURS POSTOPERATIVE	DEGREE OF POSTOPERA- TIVE REACTION (0 4+)
1	26	F.	+41	+14	13	7.5	4.2	6.0	5.9	4.2	3.7	0
2	37	F.	+40	+17	15	—	6.7	8.8	7.0	7.5	8.5	+
3	49	F.	+26	+17	16	12.0	12.3	11.3	9.7	9.0	—	+
4	58	M.	+33	+20	11	10.1	6.5	7.0	6.7	6.5	6.3	+
5	33	M.	+57	+29	19	9.5	8.3	9.3	8.0	8.0	8.4	+
6	50	F.	+45	+38	28	10.0	11.1	13.5	10.0	11.0	10.8	+++
7	41	F.	+57	+21	13	7.9	6.1	8.9	9.0	9.5	10.0	++
Average.....						9.5	7.4	9.3	8.0	7.9	7.9	

the case of the thyroid storm an entirely new clinical picture is produced which has no relation to the phenomena of thyroid insufficiency as we have come to know them. It must be stated that the explanation of the thyroid storm as an acute thyroid insufficiency has not been established.

Others have sought in the central nervous system, particularly in the diencephalon, for the precipitating factor in the genesis of the thyroid storm. Morphologically, at least, there has been no evidence that the nervous system is primarily involved. Certainly no significant changes of an etiologic nature have been demonstrated in the brain to account for the explosive reaction we call a storm, nor in fact, have any significant, constant changes which have etiologic importance been found in the central nervous system in Graves' disease. We agree with Foss and his co-workers (6) that although the liver and the heart are involved in Graves' disease

neither of them play an etiologic role in the development of the thyroid storm.

We have followed a group of patients suffering from Graves' disease in the pre-operative and postoperative periods. Determinations of the blood iodine were made and typical results are given in the following table. We are detailing only the values for the non-dialyzable iodine as all these patients received Lugol's solution after the original blood iodine levels and the basal metabolic rate had been determined.

DISCUSSION

A study of the protocols reveals the following:

1. The blood iodine level is elevated in untreated Graves' disease.
2. Treatment with iodine tends to lower the blood iodine coincident with clinical improvement.
3. There is a rise in the blood iodine immediately after thyroidectomy averaging 1.9 gamma per cent and there is a return to pre-operative levels 24 hours after the operation is completed in most cases.
4. It is worthy of note that in a patient who had one of the most severe reactions and whose operation had to be terminated after only one-half of the thyroid had been removed the blood iodine remained at a definitely high level—exceeding the pre-operative level by almost 4 gamma per cent and being higher at the 24 hour period than at any of the earlier postoperative intervals (case 7).

The purpose of this study was to attempt to correlate the postoperative reaction and particularly the postoperative crisis with variations in the level of the circulating blood iodine which we believe may be an index of the concentration of circulating thyroid hormone.

Obviously from this relatively small series no final conclusions can be drawn. With regard to the size of this series it must be pointed out that such data are very difficult to collect and we are not aware of any comparable study in the literature. However, we feel justified in concluding that there are no significant changes in the blood iodine after thyroidectomy in patients suffering from Graves' disease who have been properly prepared for surgery by bed rest, sedation and iodine and whose postoperative course is uneventful. It is interesting to note that, of the seven patients studied, the two whose blood iodine levels were the highest 24 hours postoperative were the same two who had the *least favorable* postoperative course.

We have had no opportunity to study a full-blown postoperative storm. Our experience is such that we may have to study more than one hundred cases before we encounter our first crisis.

SUMMARY

Seven cases of Graves' disease were studied. The blood iodine (non-dialyzable fraction) was found to be elevated in all. The blood iodine

level decreased after medical treatment coincident with clinical improvement. In most of the cases there were no significant changes in the blood iodine in the 24 hours following thyroidectomy except for a slight increase immediately after the operation. The two patients who showed the highest blood iodine values in the postoperative period were the same two who had the most unfavorable postoperative course. No real crisis was encountered in this series.

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METHYLATION OF HYDROXYL GROUPS IN TRIAZINES

STUDIES IN TRIAZINES. III

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Among the heterocyclic rings' triazine, consisting of three carbon and three nitrogen atoms, takes a unique position because of its high degree of symmetry. Its formation in the trimerization of numerous open chain cyanogen derivatives adds to its remarkable character. The triazine nucleus commands additional interest because of the recognition during the last decade of the vital importance of heterocyclic structures in the architecture of physiologically active substances such as vitamins, hormones and the prosthetic groups of enzymes. The greater lability of heterocycles as compared with the benzene ring suggests the use of heterocyclic nuclei such as pyridine, hydantoin and also triazine in synthesizing chemotherapeutic compounds that can readily be degraded and eliminated after having fulfilled their function (1). Finally, a condensed system comprising alternating triazine and diazine nuclei has been suggested as the basic pattern of proteins by Wrinch in her "cyclol theory."

For these various reasons, we have synthesized derivatives of triazine, starting from the trimethyl ester of isocyanuric acid, which is in heterocyclic terminology 1,3,5-trimethyl-2,4,6-triketohexahydrotriazine (2,3). Because of its unique structure, the carbonyl groups in this and in related compounds do not behave in all respects like keto groups. By means of Grignard's magnesium compounds, substances were synthesized which we formulate as 1,3,5-trimethyl-2-alkyl (or phenyl)-4,6-diketo-2-monohydroxy-hexahydrotriazine.



It was remarked that the hydroxyl group of the cyclic carbon between two tertiary nitrogen atoms lacks phenolic and alcoholic character; it proved inert toward diazomethane and even phenyl isocyanate.

In a recent publication Haurowitz (4) discusses the methylation and acetylation of proteins in respect to hypotheses of protein structure. His results confirm previous experiences, that the number of methyl or acetyl groups which may be introduced into proteins can be accounted for by the free hydroxyl and amino groups of a polypeptide chain. However, his

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conclusion that this fact excludes the existence of cross linkages, resulting in hydroxylated triazine nuclei cannot be upheld, since we have found that under his conditions of methylation and acetylation even a comparatively simple structure like (I) does not react at all, the starting material being recovered quantitatively from the reaction mixture.

EXPERIMENTAL

Methylation. Two hundred and fifty milligrams of (I) ($R = C_6H_5$) were suspended in 10 ml. of water and just enough five per cent sodium hydroxide added to bring it into solution; 250 mg. of dimethylsulfate were then added dropwise at room temperature under stirring; the solution remained alkaline. After two hours' standing the excess dimethylsulfate was destroyed by addition of ammonia and the mixture acidified. The white precipitate was recrystallized from benzene and melted at $161^\circ C$. The mixed melting point with the starting material was 160 to $161^\circ C$.

Acetylation. Five hundred milligrams of (I) ($R = C_2H_5$) were refluxed with 2 ml. of acetic anhydride for two hours. After cooling, the solution was poured on ice and the aqueous solution extracted several times with ether. After washing and drying, the ethereal extract was evaporated and the residue recrystallized from absolute ether. The melting point was $113^\circ C$. The mixed melting point with the starting material was $113^\circ C$.

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SYPHILITIC AORTITIS WITH AORTIC REGURGITATION

AN ELECTROCARDIOGRAPHIC AND AUTOPSY SURVEY AT THE MASSACHUSETTS GENERAL HOSPITAL

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A survey of the various types of heart disease in New England (1) has revealed that rheumatic heart disease comprises about forty per cent of the cases, and syphilitic heart disease, only about 4 per cent. With such a high incidence of rheumatic valvular disease, it is natural that the differential diagnosis between syphilitic and rheumatic involvement of the aortic valve should frequently come into question in this part of the country. While the correct diagnosis is usually made without great difficulty, all diagnostic aids are at times required, and a combination of the two infections in the heart is sometimes found at autopsy. At the Massachusetts General Hospital, typical syphilitic aortitis with or without aortic regurgitation is becoming a relatively rare disease, certainly so far as our autopsy experience is concerned.

The present report is based on the 5,044 autopsies of the years from 1925 to 1941. In these sixteen years, it was possible to collect only 22 cases of syphilitic aortitis in which the clinical diagnosis of aortic regurgitation was made, the serology was positive,¹ electrocardiographic study was made, and the autopsy performed. In some of these cases the diagnosis finally rested on the microscopic as well as the gross examination of the aorta. Such examples, therefore, cannot be considered characteristic of the fully developed aortic regurgitation of syphilis, but it is just such cases which present the most difficult differential diagnostic problems. While autopsy examinations give precise correlation between the clinical findings and anatomical distortions, they do not necessarily give a complete picture of a particular disease. This is in part due to the fact that unusual and puzzling cases are those for whose post-mortem examinations a greater effort is made, and it is not expected that these figures will necessarily be representative of the general autopsy experience in Boston.

The question of most concern to the author is the degree to which the electrocardiograph could serve as a guide to the possible complications of syphilitic aortitis and aortic regurgitation. Several excellent studies

¹ In one instance of typical syphilitic aortitis, the patient died before the blood serology was obtained.

of this have already appeared (2, 3, 4, 5, 6). In some of these autopsy correlation was not possible and there is, perhaps, no cardiovascular condition in which more surprises at the autopsy table may appear. In general, electrocardiographic studies have indicated that the electrocardiograph does not show changes which can be considered specific for syphilis of the heart. Conduction defects, both auriculo-ventricular and intra-ventricular have been described as well as S-T displacements and T wave inversions in all of the leads. A high percentage of electrocardiographic abnormality is to be expected. In Juster and Pardee's (5) series, abnormal electrocardiographic features were found in 78 per cent. Abnormal rhythms may occur, such as auricular fibrillation, auricular flutter and premature beats. In the presence of aortic regurgitation with left ventricular hypertrophy, and relative anoxia of the heart, left axis deviation is the usual change. Authors also note that the common complications of hypertension and coronary atherosclerosis introduce confusing electrocardiographic signs.

In the series reported here, there were 22 cases, 20 males and 2 females. The age range was from twenty-six to seventy-four years. Complications were extremely common. These were as follows: hypertension, 10 cases; arteriosclerotic coronary disease, 3 cases, in 2 of which there was myocardial infarction; rheumatic heart disease alone, 2 cases; bacterial endocarditis alone, 1 case; a combination of congenital heart disease, rheumatic heart disease, and subacute bacterial endocarditis, 1 case; aneurysm of the aorta, single or multiple, 11 cases. In fact, it was difficult to find localized and uncomplicated syphilitic aortitis with aortic regurgitation. Including cases with hypertension and the 1 case with bacterial endocarditis, there were only 4 cases of syphilitic aortitis uncomplicated either by aneurysm or other abnormality.

ELECTROCARDIOGRAPHIC FINDINGS

Left axis deviation. The origin of the present investigation depended, in part, upon the fact that left axis deviation in the presence of aortic regurgitation was not found so frequently as might be expected if the electrocardiogram were reflecting an uncomplicated strain upon the left ventricle. In this series there were 7 instances of typical left axis deviation, although in three of these cases the left axis deviation was only slight. In these 7 cases hypertension was present in 4. In one other instance, a man of sixty-seven, the disease was mild but of long standing with calcification of the aorta, and a heart weight of 570 grams. In the sixth case the heart was small, weighing only 295 grams with only a slight aortic diastolic murmur discovered during life. There was, however, a fusiform dilatation of the aorta. In the seventh case there were faint systolic and diastolic murmurs over the aortic area. Autopsy showed no separation of the commissures of the aortic valve, but a slight adhesion of the cusps, and a left ventricle

twice normal in size, with narrowing of the right coronary orifice. In this group with left axis deviation, further electrocardiographic changes were low voltage, delayed auriculo-ventricular conduction, sagging S-T intervals in leads I, II and III, auricular premature beats, sinus tachycardia, independent auricular and ventricular rhythms, inversion of T₁ and T₄, with low S-T take-off in lead IV, and notching of QRS. The coronary orifices were noted as narrowed on the left in one case, on the right in two cases, and occlusion of the descending branch of the left coronary was found in the one case of myocardial infarction which also presented hypertension.

It will be seen from this description that only about one-third of these 22 cases had an expected left axis deviation in the electrocardiogram in spite of aortic regurgitation, definitely diagnosed during life. There remain 15 cases in which the electrical axis was either normal or deviated to the right, or in which there was intraventricular block of varying types. There were 4 instances of the latter condition.

Right bundle branch block. Two cases showed right bundle branch block. In one of these, a single observation of hypertension was made, but in addition there was a very large aneurysm of the arch of the aorta which finally ruptured into the pulmonary artery as the terminal event. No coronary narrowing was found in this case. The other case also showed hypertension with saccular aneurysm of the ascending aorta, and marked coronary arteriosclerosis and narrowing. In both of these examples of right branch defect, the electrocardiogram was of the S₁ type, and the ventricular complexes were not widened beyond 0.12 second.

Left bundle branch block. There was one instance of left bundle branch block. The patient entered in extremis with auricular fibrillation, and a diagnosis of angina pectoris with coronary occlusion was made. Autopsy showed a complete occlusion of the right coronary orifice from syphilitic aortitis but there was no myocardial infarct or aneurysm of the aorta.

Atypical bundle branch block. There was one example of intraventricular block of the indeterminate type. In this case, there were multiple aneurysms of the aortic arch with rupture of one of these into the pulmonary artery. The physical findings were then altered by the development of a marked dilatation of the pulmonary artery with a continuous murmur over it. This led to the diagnosis of the rupture; the condition was survived for eight months more, and confirmed by autopsy. There was, in addition, complete occlusion of the right coronary orifice.

Right axis deviation. Two cases had right axis deviation. Such a finding should always make one suspicious of a complicating strain upon the right heart. This might, most commonly, be expected to be due in New England to a complicating rheumatic heart disease with mitral stenosis. It might also be due to *cor pulmonale* either in its acute stage from pulmonary infarction, or in the more chronic stage from pulmonary

endarteritis, perhaps due to syphilitic involvement of the vessels from the so-called Ayerza's disease. We have not observed this in our cases. One patient, a man aged forty, showed marked dilatation of the right heart at autopsy, with rheumatic mitral disease and insufficiency of the valve without stenosis and an acute endocarditis of all the valves of the rheumatic type. The aortitis was of an unusual nature, but there was separation of the commissures of the aortic valve and, microscopically, the aorta was considered to be syphilitic. In the other case, a man aged fifty, there was hypertrophy of the right auricle and right ventricle, with acute endocarditis of aortic and mitral valves, and chronic endocarditis of the mitral valve with marked mitral stenosis of the rheumatic type. There was also an acute pericarditis. The right coronary orifice was very small. In addition to the right axis deviation in the electrocardiogram, the P wave was notched, and the P-R interval was 0.2 second.

Normal electrical axis. There remain for consideration nine instances or almost half of the cases in which the electrical axis was normal. In the presence of aortic regurgitation, such a finding is worthy of analysis because it suggests a condition of the heart in which either there is little strain on the left ventricle, or there is some compensating factor of right heart strain or anoxia resulting in preponderance or conduction effects balancing the left-sided shift. Briefly, the findings in these 9 cases were as follows:

1) Male, 44. There was a large aneurysm just above the sinuses of Valsalva pressing on and displacing the pulmonary conus. It exerted pressure also on the left auricle, and on the left bronchus resulting in collapse of the left lower lobe. The final event was rupture into the pulmonary artery and the pericardium. Auricular flutter was present at times, and at other times sinoauricular bradycardia with sagging S-T intervals due to digitalis, and deep inversion of the T waves in leads I and II. Autopsy disclosed that the aortic valve was apparently not involved in the syphilitic process; there was no evidence of separation of the aortic commissures. This is an instance in which well marked aortic regurgitation with Corrigan pulse and other peripheral signs were present from a dilatation of the aortic ring. The coronary arteries were not involved. The heart weight was not determined as there were 1,000 cc. of blood in the pericardial cavity.

2) Male, 64. There were multiple aneurysms of the aorta with final rupture into the mediastinum and the esophagus. The coronary arteries were sclerotic but patent. Although the aortic diastolic murmur was described as moderately loud, the aortic valves and commissures were not involved, and the heart weighed only 340 grams with slight prominence of the left ventricle. The T wave was flat in lead I. This may be considered another example of functional aortic regurgitation, due to the aortitis without involvement of the aortic valve.

3) Male, 56. A loud aortic diastolic murmur was heard, but by x-ray examination the heart was reported as normal in size. Autopsy, however, showed moderate cardiac enlargement with syphilitic aortitis and separation of the aortic cusps, but also a fresh vegetative endocarditis with perforation of one of the aortic cusps. Culture of the vegetations showed *B. subtilis*, and *B. coli*. The T waves were low in the electrocardiogram. In this case, the aortic regurgitation was probably only slight until the final ulcerative involvement of the aortic valve, and not enough time elapsed before death to result in much strain upon the left ventricle.

4) Male, 29. This man gave a history of rheumatic fever at the age of fourteen, and heart disease was diagnosed at that time. For eight or nine months before he was seen, he had had typical angina pectoris on effort, and also at rest. The clinical diagnosis was rheumatic heart disease with aortic regurgitation and slight mitral regurgitation, and mitral stenosis. He died suddenly following paravertebral alcohol injection for his intractable pain. Autopsy showed syphilitic aortitis with separation of the aortic commissures and complete occlusion of the right coronary orifice. No involvement of the mitral valve was found, and no evidence of rheumatic heart disease. Electrocardiogram showed a low T wave in lead I with inverted T waves in leads II and III. The heart weighed 559 grams. It is possible in this instance that the aortitis was relatively acute to account for the absence of the left axis deviation. A conduction defect may have played a part in the balance of the electrical axis.

5) Male, 26. In this case, the process was acute. A small aneurysm was found in one of the sinuses of Valsalva with a rupture of an attachment of one aortic cusp. The left coronary orifice was narrowed. A suspicion of syphilitic myocarditis was also raised on microscopic examination of the heart muscle. The heart weighed only 375 grams and by x-ray examination, did not have an aortic shape. Electrocardiogram showed inversion of T waves in leads I and II. Here again, the acuteness of the process was probably responsible for the absence of the signature of left ventricular strain in the electrocardiogram.

6) Male, 40. Multiple aneurysms of the aorta with stenosis of the right coronary orifice were found at autopsy. In spite of a loud double aortic murmur described in the physical examination the aortic valve was not involved and the heart was normal in size, weighing 350 grams. This is another example of relative aortic regurgitation with aneurysm, without involvement of the valve. A Corrigan pulse was described, and also the peripheral signs of aortic regurgitation. The T wave was low in lead I.

7) Male, 51. Although some hypertension was noted, 184 systolic and 74 diastolic, the aortic diastolic murmur was described as faint. Autopsy showed slight separation of the aortic commissures but the heart weighed only 300 grams. No aneurysms and no coronary involvement were found. The electrocardiogram showed a low T_1 and T_2 , with inverted T_3 . In

this instance, one would have expected to find some left axis deviation in the electrocardiogram from the hypertension alone; however, it is not known how long this existed. It is interesting that again no separation of the aortic commissures was found.

8) Male, 68. On one occasion, hypertension was noted in the examination. In addition, the patient had pernicious anemia and a healed myocardial infarct with calcified aneurysms of the subclavian and innominate arteries. The heart weight was 550 grams. Electrocardiogram showed slight inversion of the T wave in lead I. It is possible here that a conduction defect in the ventricles prevented the ordinary picture of left axis deviation, and was related to the myocardial infarction.

9) Male, 37. The condition found at autopsy in this case was the most complicated in the entire series. Autopsy showed rheumatic heart disease with aortic stenosis, as well as syphilitic aortitis, and a congenital interventricular septal defect. These abnormalities were further complicated by a subacute bacterial endocarditis. There was marked hypertrophy of both ventricles. The heart weighed 650 grams. The diagnosis of all the conditions except the septal defect was made clinically. Electrocardiogram showed sagging S-T intervals. Undoubtedly, in this instance, the balance of strain on both ventricles resulted in a normal electrical axis.

DISCUSSION

Within the compass of this relatively small series of cases of syphilitic aortitis, there are examples of most of the complications which might be expected to alter the contour of the electrocardiogram. This study would confirm the findings of others, that the S-T and T wave changes are not specific for this condition. Table I shows the total incidence of the electrocardiographic abnormalities in this series. In well-marked aortic regurgitation of long standing, one may expect the electrocardiographic picture of left ventricular strain, or relative ischemia. It would appear that absence of this finding as well as other alterations in the QRS complex would be more suggestive of a complicating factor or an atypical situation. While the series is too small to assure any consistency in these findings, the following observations were made. In the cases with bundle branch block, marked coronary narrowing or obstruction was found in 3 out of 4 cases, and in 2 cases, aneurysms of the aortic arch exerted pressure on the pulmonary artery and finally ruptured into it. This rupture was survived by 1 case for at least 8 months, and the type of bundle branch block was not clearly right or left.

Two cases showing right axis deviation were both complicated by rheumatic heart disease, one with marked mitral regurgitation, and the other with marked mitral stenosis. When a normal electrical axis was found, the following complicating conditions were also present which were apparently responsible for the lack of left axis deviation, even in the presence

of aortic regurgitation: congenital heart disease; rheumatic heart disease; acute aortitis with bacterial involvement and rupture of an aortic cusp; atypical aortitis with rupture of an attachment of an aortic cusp; aneurysm of the aorta with functional aortic regurgitation; chronic pressure on, and displacement of the pulmonary artery and left auricle from aneurysm;

TABLE I

TOTAL INCIDENCE OF ELECTROCARDIOGRAPHIC FINDINGS	NO. OF CASES
Total.....	22
Left axis deviation.....	7
Right axis deviation.....	2
Right bundle branch block.....	2
Left bundle branch block.....	1
Intraventricular block (indefinite).....	1
Long P-R interval.....	3
Inverted T ₁	6
Low T ₁	3
Low T all leads.....	2
Inverted T ₁ and T ₂	2
Inverted T ₂ and T ₃	1
S-T displacements—sagging (some due to digitalis).....	6
Notched QRS.....	2
Independent auriculo-ventricular rhythms.....	1
Auricular fibrillation.....	1
Auricular flutter.....	1
Auricular premature beats.....	1
Ventricular premature beats.....	1

bronchial obstruction; myocardial infarction; and absence of an enlargement of the heart.

CONCLUSIONS

A series of 22 cases of syphilitic aortitis with aortic regurgitation autopsied at the Massachusetts General Hospital from 1926 to 1941 has been analyzed with reference to the electrocardiographic findings. The absence of left axis deviation in the electrocardiogram suggests a complication beyond simple aortic dilatation with involvement of the aortic cusps and separation of their commissures. Conditions resulting in acute, or chronically mild strain on the left ventricle, or conditions resulting in an additional strain on the right ventricle appear to be largely responsible for the appearance of a normal electrical axis or a right axis deviation. In cases with bundle branch block, high degrees of coronary obstruction may be present, particularly of the right coronary orifice. But in one case without coronary narrowing, a large aneurysm pressing on and finally perforating into the pulmonary artery was found at autopsy. It is suggested

that the electrical axis of the electrocardiogram is of more use than the S-T and T segments in indicating complications of syphilitic aortitis.

The results of this study afford another example of the fact that the extent of disease and the presence of complications are often of more importance than an etiologic factor alone in the production of alterations in the electrocardiogram.

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COMPARISON OF SIMULTANEOUS INDIRECT (AUSCULTATORY) AND DIRECT (INTRA-ARTERIAL) MEASUREMENTS OF ARTERIAL PRESSURE IN MAN¹

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The accuracy of the indirect method of measuring arterial pressure in human beings by means of placing a pneumatic cuff about the upper arm and auscultating the sounds arising in the artery below it (1) has until recently been difficult to test. Application of Frank's principles of direct intra-arterial manometry (2, 3) to smaller and less sensitive manometers (4, 5) whose sensitivity is subsequently magnified by using longer beams of light, has permitted the use of cannulae for connecting artery and manometer of such small caliber that ordinary luer needles (18 to 25 gauge) may be employed. Finally, substitution of short pieces of flexible lead tubing for the older rigid metal ones to connect arterial cannulae to the manometers has made the positioning of subject and manometer so convenient that direct intra-arterial measurement of pressure in various arteries, often in two or three arteries simultaneously, of unanesthetized man and beast may be carried out without pain and with minimal disturbance. In individuals whose flesh is especially tender, arterial puncture may, in fact, often be performed with less discomfort than that which accompanies inflation of the cuff for measuring arterial pressure by the usual indirect technique.

In view of these advances in technique, it seemed desirable to compare measurements of arterial pressure obtained by the usual indirect technique with those obtained by an established direct method in order to furnish data for rational criteria for the use of the usual auscultatory technique. The instrument developed by Hamilton (4) was chosen.

Procedure. The patient is placed supine in bed, the arm supported horizontally at an angle of about 60° to the axis of the body on a small padded frame which supports the arm from elbow to wrist and at the same time allows clearance for inflation of the pneumatic cuff about the upper arm. The cuff is connected by the two arms of a Y-tube to a mercury manometer and to one of two Hamilton manometers. The needle of the second Hamilton manometer is inserted into the radial artery. The cuff is then inflated and deflated in the usual manner for estimation of arterial

¹ The latter part of this investigation has been aided by a grant from the Josiah Macy, Jr. Foundation.

pressure by listening for Korotkoff sounds with a stethoscope, while pressures in the radial artery and within the cuff are being simultaneously recorded by optical means. Note is made of the level of the mercury manometer at the appearance of sound, at the moment of sudden muffling and at the disappearance of sound (first, fourth and fifth phases respectively), and their occurrence is signalled on the photographic record.

With the help of these records, the systolic and diastolic pressures recorded by the Hamilton manometer may be compared with those estimated at the various phases with the help of Korotkoff's sounds by reading the level of the mercury manometer. The level of pressure in the pneumatic cuff may also be estimated for these points from the optical record, and thus serve as a guide to the correctness of the mercury manometer in indicating the pressure within the cuff. Observations obtained show that the effective size of the vent at the top of the mercury manometer is the factor which limits the speed at which the cuff can be deflated without lag in recording the pressure therein. With the manometers in general use, the pressure in the cuff may be lowered as rapidly as 8 mm. per second without significant loss of accuracy. It is, however, important to note that the distance in millimeters of mercury which the manometer drops between two beats contributes to error. This error is directly proportional to the rate of fall and inversely proportional to the pulse rate. Hence, a slow rate of fall (3 to 5 mm. per second) in passing the levels of systolic and diastolic pressure, is desirable. Although the differences between measurements of pressure in the cuff by the Hamilton and by the mercury manometer are small, they are significant and this phase of the problem is still under investigation.

The accuracy of the measurements obtained from the optical records of the direct manometer seems unquestionable in theory. Certain practical difficulties leave room for error. In order to avoid these errors so far as possible, the following precautions have been taken: 1) The frequency of the manometers has been tested regularly and records were not used unless the frequency was greater than 150 per second. 2) A needle of smaller caliber or of greater length than the one with which the manometer was calibrated was never used. 3) After insertion of the needle into an artery, it was ascertained that moderate changes in its position did not affect the character or amplitude of the pulse wave. 4) When the needle was withdrawn after the recording was complete, its point was examined for partial blocking by clot or by bits of tissue and, if present, the record was discarded. The patency of the needle was also ascertained by forcing citrate solution through it under pressure. A defect in the smooth ejection stream was readily observable.

Comparison between the two methods has been made 74 times in 39 individuals selected only in that they did not exhibit valvular defects or arrhythmias (Table I). Each comparison involves two separate successive

TABLE I

Comparison of direct and indirect arterial pressures in forty-one individuals are made. Direct manometer is in right radial artery. Standard pneumatic cuff (12 cm. wide), about right brachial artery.

PATIENT	SYSTOLIC PRESSURE MM. Hg			DIASTOLIC PRESSURES MM. Hg				
	Auscultatory	Direct manometer	Difference*	Auscultatory		Direct manometer	Differences*	
				4th phase	5th phase		4th phase	5th phase
1. E. K.	130	130	0	86	80	75	+11	+5
2. A. S.	124	128	-4	—	76	72	—	+4
3. R. B.	94	96	-2	68	60	58	+10	+2
4. R. S.	150	162	-12	80	70	74	+6	-4
5. R. S.	185	170	+15	114	110	112	+2	-2
6. C.	210	215	-5	—	130	132	—	-2
7. R. K.	156	164	-8	—	106	108	—	-2
8. H. S.	200	230	-30	140	130	130	+10	0
9. L. R.	234	255	-21	140	126	125	+15	+1
10. W. N.	214	242	-28	—	140	142	—	-2
11. E. T.	115	112	+3	75	69	70	+5	-1
12. A. S.	114	125	-11	80	76	82	-2	-8
13. A. S.	148	156	-8	—	80	73	—	+7
14. J. B.	115	119	-4	80	72	68	+12	+4
15. H. M.	241	242	-1	—	120	122	—	-2
16. J. W.	112	136	-24	—	84	78	—	+6
17. M. K.	152	192	-40	—	92	88	—	+4
18. W. J.	122	149	-27	90	80	80	+10	0
19. J. S.	210	212	-2	140	130	128	+12	+2
20. R. S.	130	146	-16	—	73	70	—	+3
21. T. R.	113	115	-2	67	60	62	+5	-2
22. D. S.	170	196	-26	—	92	90	—	+2
23. J. M.	142	126	+16	106	86	80	+26	+6
24. J. N.	120	125	-5	—	80	83	—	-3
25. T. R.	112	120	-9	—	61	58	—	+3
26. W. J.	114	135	-21	—	69	70	—	-1
27. J. B.	122	126	-4	70	68	62	+8	+6
28. R. S.	122	145	-23	68	60	52	+16	+8
29. S. S.	262	270	-8	—	164	164	—	0
30. L. C.	126	149	-23	—	78	80	—	-2
31. J. F.	160	159	+1	—	80	79	—	+1
32. L. H.	162	184	-22	88	84	89	-1	-5
33. A. B.	116	126	-10	74	68	68	+6	0
34. W. S.	129	131	-2	90	80	82	+8	-2
35. E. G.	131	138	-7	72	68	63	+9	+5
36. J. H.	144	170	-26	86	80	90	-4	-10
37. J. C.	163	156	+7	78	74	75	+3	-1
38. J. P.	144	146	-2	96	92	86	+10	+6
39. G. B.	150	152	-2	92	86	81	+11	+5
Average.	150	160	-10	90.1	88	87.3	+8.8	+0.8
40. P. O.	138	150	-12	70	50	50	+20	0
41. J. D.	108	139	-31	70	45	67	+3	-22

* Differences are recorded with the direct record as a standard.

simultaneous measurements by each method. In ten individuals, two comparisons were made. The ages ranged from 22 to 86 years. Twenty-one were normal, seven suffered from arterial hypertension alone, three from hypertension and arteriosclerosis, and eight from arteriosclerosis alone. Two were quite obese. It is obvious that the number of patients in each group is, as yet, far too small to bring out clearly the limits of the indirect method. Although the data are not yet sufficient to permit describing rules for estimating arterial pressure by the indirect method of Korotkoff, they suggest that revision of the present empiric criteria (6) may be necessary when sufficient data have been obtained. Certain tendencies are of interest.

After the pulse wave in the record of arterial pressure from the radial artery has been obliterated by inflating the pneumatic cuff about the upper arm to a pressure above systolic level, pressure within the artery distal to it falls below the usual diastolic level. As the pressure in the cuff is lowered gradually, the first or second (fig. 1 A, B, C), rarely the third, beat (fig. 1 D) to become visible in the arterial record is audible; which one becomes audible appears to depend partly upon the speed of deflation and partly upon the form of the pulse wave. Of interest is the fact that the systolic level recorded by the Hamilton manometer immediately after release of the cuff is often elevated by 6 to 12 mm. Hg. for about 10 seconds and consequently the level during this period was not used for comparison.

The beat which is audible or visible usually occurs below the systolic level of pressure recorded in the radial artery by the Hamilton manometer (Table I and fig. 2). There does not appear to be any greater difference for high, than for low pressures. The average systolic level obtained by auscultatory technique is, for the present data, 10 mm. Hg. below that obtained by the intra-arterial measurements.

It seems to be generally believed that diastolic pressure is more difficult to record than systolic; but when the diastolic pressures taken by the auscultatory method are compared to those measured directly, the differences between the two appear to be less than those obtained in measurements of systolic pressure and of opposite sign. When the fifth phase (disappearance of sound) is used, the average difference between auscultatory and direct readings is negligible (less than 1 mm.). When the fourth is used, the auscultatory level averages 8.8 mm. higher than the direct. In only three instances was the diastolic pressure closer to the direct reading at the fourth phase, than that at the fifth (Table I, fig. 2). When muffling and disappearance of sound take place almost simultaneously, the single pressure has been recorded in the column labelled "fifth phase". The data indicate that the disappearance of sound, except in the case of aortic insufficiency, is a more accurate guide to diastolic pressure than the sudden muffling recommended by the English component of the Committee for Standardization of Blood Pressure Readings (6) and by Bramwell (7).

Two observations with regard to diastolic pressure in aortic insufficiency have been made. In one, the fifth phase of Korotkoff's sound is the better estimate of diastolic level (Case 40 and fig. 3) and in the other, the fourth (Case 41). Sound often persists, when this valvular lesion is present, until the cuff is completely deflated indicating a pressure of zero, which is obviously unlikely.

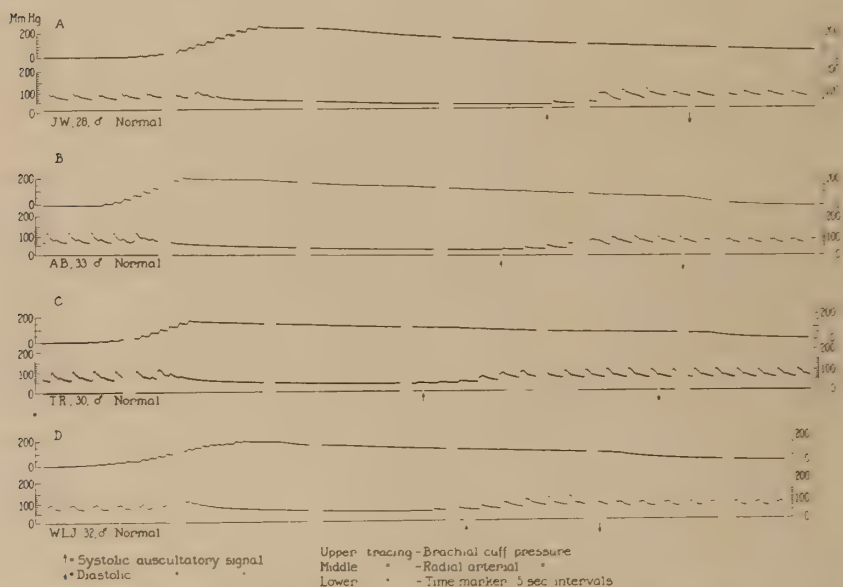


FIG. 1. Optical records of arterial pressures in the right radial arteries of four normal individuals during compression of the brachial artery by a pneumatic cuff are shown.

	DIRECT PRESSURES		AUSCULTATORY PRESSURES	
	Systolic	Diastolic	Systolic	Diastolic
A	125	80	112	84
B	116	68	126	68
C	115	62	113	60
D	122	90-80	149	78

The beat immediately preceding the arrow pointing upward is the first audible beat. Reduced to one-quarter the original size.

The divergence of the two methods in systolic pressure invites discussion. Part of the difference is easily accounted for by two well recognized facts. First, systolic pressure is higher in the radial than in the brachial artery. Woodbury, Murphey and Hamilton (8) gave differences of 8 and 9 mm. Hg in a normal individual and in a case of coarctation of the aorta respectively for the difference between the *axillary* and radial arteries. The difference

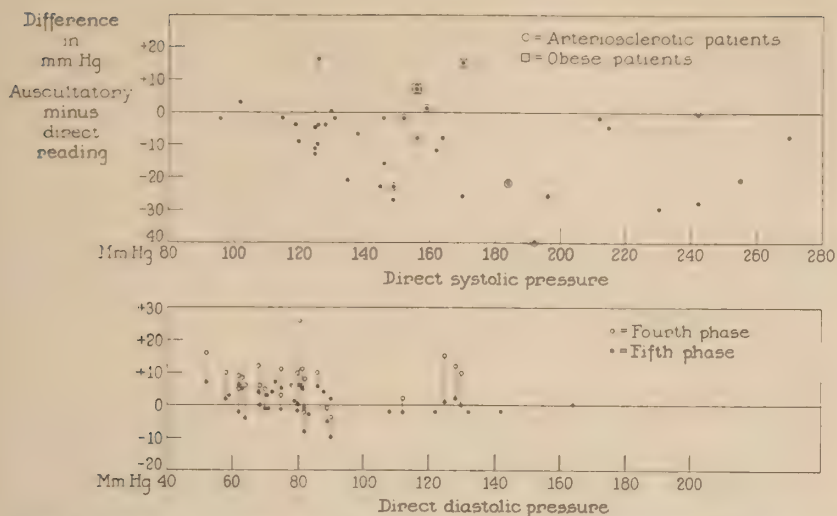


FIG. 2. The data contained in Table I are represented graphically. Instances in which the auscultatory measurements coincide with the direct, fall on the zero line. When a point falls below or is above the zero line, the vertical distance from the line represents the degree to which the auscultatory measurement either falls short of or exceeds the direct measurement.

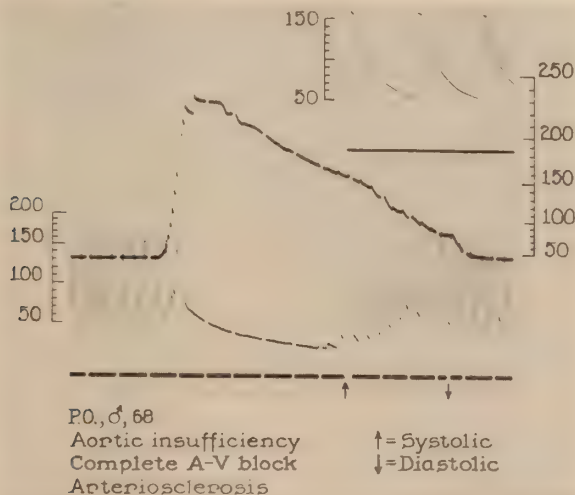


FIG. 3. Optical records of the movements of two Hamilton manometers are shown. The lower tracing records arterial pressure in the right radial artery (left hand scale); the upper tracing, pressure changes in the pneumatic cuff around the brachial artery while it is being inflated and deflated (right hand scale). Direct pressure levels recorded are systolic 150; diastolic 52 mm. Hg; auscultatory pressure levels are systolic 148; diastolic, 4th phase, 70, 5th phase, 50 mm. Hg.

should be less between the *brachial* and radial arteries. In the one instance in which the author has measured this difference it amounted to 5 mm. Hg. Secondly, unless the first beat at systolic level is heard, an additional error

in the same direction will be made, an error which depends on the rate of the pulse and the speed with which the mercury column is falling. In the present studies, this error probably varied from 3 to 6 mm. Hg. A correction for these two factors would account for the observed differences in roughly half of the cases (those below 10 mm. Hg. difference).

Concerning the larger differences, Robinow, Hamilton, Woodbury and Volpitto (9) and Bordley (10) have suggested that the form of the pulse wave may have a bearing upon the question. Those with sharp peaks, a form which suggests small changes in volume at high pressures, are the ones which tend to give lower auscultatory readings in relation to the direct readings. Bordley suggests that the pressure wave resulting from the

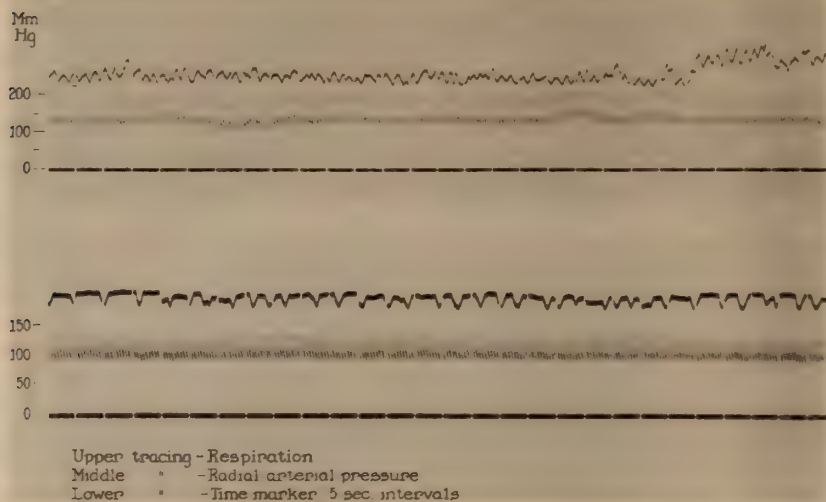


FIG. 4. Optical records of respiration and arterial pressure in the radial arteries of two elderly individuals while lying quietly during a long study are shown. The portions selected are representative fractions of continuous tracings obtained over periods lasting for more than twenty minutes to show changes in levels of pressure, some of which appear to be synchronous with respiratory rhythm and some of which do not.

smaller volume may be more readily damped in passage under the cuff. The present data fit in, for the most part, (fig. 1 A and B compared with C) with this view, but exceptions occur. Two of the six instances in which systolic pressure was, contrary to the usual experience, estimated to be at a higher level by the auscultatory than by the direct method, were in extremely adipose individuals. The relation between size of cuff and size of arm in these cases deserves careful study and involves diastolic as well as systolic pressures. Observations in several individuals during a long period of loss of weight (11) tend to show that larger cuffs do, in some obese people, give lower readings for arterial pressure than the standard cuff yields and more nearly approximate the levels obtained with direct measurement.

The other four observations in which the auscultatory technique yielded a higher pressure than the direct, occurred in individuals with arteriosclerosis, and yet arteriosclerosis was also present to a marked degree in at least four individuals in whom the error was large in the usual direction (fig. 2). An additional obvious reason for discrepancy between the two methods is the continual variation of both systolic and diastolic pressure not only with respiration (fig. 4) but also independently of respiration. These latter variations may correspond to the phasic changes in blood flow described by Burch, et al. (12) or to Traube-Hering waves. Whatever the reason for the change in level, it is clear that the indirect method singles out one beat, the first one to force its way through the cuff, while the direct method records a succession of beats. Measurements of the range of variability of arterial pressure are being carried out and will probably help to explain in part the differences between the methods but cannot do so entirely for the reason that the order of magnitude of the spontaneous variations is usually only from 5 to 10 mm. Hg.

In the case of diastolic pressure, the systematic discrepancies due to difference in site of measurement do not occur. Woodbury, Murphey and Hamilton's measurements (8) as well as my own observations failed to show significant differences in diastolic pressure along the course of the brachio-radial artery. In addition, respiratory and other variations of diastolic pressure are less with the result that direct and indirect diastolic measurements agree more closely.

SUMMARY

Concerning the comparison of simultaneous measurements of arterial pressure obtained by direct intra-arterial manometry and by indirect auscultatory technique in 39 individuals, it may be said that:

1. Systolic pressure was underestimated in indirect measurement by about 10 mm. Hg. In the present study, the indirect pressure in the brachial was compared with the direct pressure in the radial artery. This procedure may account for half of this difference.

2. In auscultatory technique the disappearance of sound proved to be a more accurate measure of diastolic pressure than the sudden muffling. The former over-estimated diastolic pressure by 8.8 mm. Hg., the latter by less than one.

3. The indirect auscultatory method of estimating arterial pressure is, considering its convenience and simplicity, an unusually accurate bedside method.

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THE PERIPHERAL BLOOD FLOW IN TEN WOMEN EXHIBITING GRAVES' DISEASE

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The cardiac output (1), the circulating blood volume (2), the velocity of blood flow, the pulse rate and pulse pressure (3) are increased, and the vital capacity (4) decreased when the basal metabolism (5) is elevated in thyrotoxicosis. The hot flushed skin of patients suffering from Graves' disease has been interpreted as due to increased peripheral blood flow.

Since there are clinical evidences of increased peripheral blood flow in Graves' disease, objective measurements were considered desirable. These data have now been accumulated and form the subject of this report. The velocity of blood flow, the blood pressure and the pulse rate have also been recorded in order to have other objective measurements to correlate with peripheral blood flow. This study concerns 10 patients suffering from typical Graves' disease. Selection was made in order to secure patients as nearly alike as possible in their manifestations of thyrotoxicosis. All subjects were women exhibiting normal sinus mechanism without signs and symptoms of congestive heart failure. The surgical pathologic diagnosis of the removed gland in each case was "diffuse hyperplastic goitre."

METHODS

Measurements of peripheral blood flow were made using a modification of the method of Hardy and Soderstrom which has been described elsewhere (6). In order to use this method, certain data were required, namely: recordings of skin temperature, of rectal temperature, of oxygen consumption, of height and of body weight. In addition, the blood pressure, the pulse rate, and the arm to tongue circulation time were recorded. The arm to tongue circulation time was measured by the use of Decholin (7).

PLAN OF OBSERVATIONS

The order in which data were recorded followed the plan outlined elsewhere (6). Six sets of skin and rectal temperatures, at twenty minute intervals, appeared to be sufficient, and from these recordings five average periods of peripheral blood flow were calculated. The blood pressures

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and pulse rates were recorded during free intervals between temperature readings. The arm to tongue circulation time was measured after the last oxygen consumption had been estimated. Observations subsequent to the initial phase were made in exactly the same sequence for each patient under the controlled environmental temperature (6). Throughout this paper when the terms "Before Iodine", "During Iodine" and "After Operation" are used they indicate that the patients were first studied before the administration of iodine, while receiving iodine therapy, usually

TABLE 1
Summary of data relating to 10 patients suffering from Graves' disease

	BEFORE IODINE			DURING IODINE			AFTER OPERATION		
	Highest	Lowest	Average	Highest	Lowest	Average	Highest	Lowest	Average
Basal metabolic rate (per cent).....	+67	+21	+44	+48	+7	+25	+19	-1	+10
Peripheral blood flow (cc./M ² /min.).....	281	156	193	225	86	121	117	31	60
Average skin temperature (°C.).....	35.24	33.43	34.41	34.90	31.67	33.73	34.48	30.53	33.23
Temperature of hands (°C.)...	35.50	34.00	35.02	35.20	32.60	34.28	35.30	32.70	34.26
Temperature of feet (°C.)...	34.60	31.20	33.08	33.80	25.90	31.49	33.30	26.40	29.92
Rectal temperature (°C.)....	37.58	37.01	37.31	37.48	37.05	37.22	37.51	37.09	37.25
Pulse rate (per min.).....	115	87	104	91	70	83	85	63	75
Pulse pressure (mm. Hg)...	68	38	55	68	34	48	75	34	42
Circulation time (seconds)	10.6	7.1	8.8	12.9	8.2	10.4	17.4	10.2	12.9

1 to 2 days before operation, and in the latter part of their postoperative convalescence from subtotal thyroidectomy, respectively.

RESULTS

Basal metabolic rate and peripheral blood flow. In the phase "Before Iodine" when the basal metabolic rate was high, the peripheral blood flow was also elevated. "During Iodine" fall in basal metabolic rate and peripheral blood flow from the initial levels occurred. Finally, in the phase "After Operation" further decrease in basal metabolic rate and peripheral blood flow was observed (Table 1) (fig. 1).

Skin temperature. The average skin temperature was high at first,

decreased during the administration of iodine, and fell further still after subtotal thyroidectomy. The average temperature of the hands and feet showed similar trends for the whole group (Table 1).

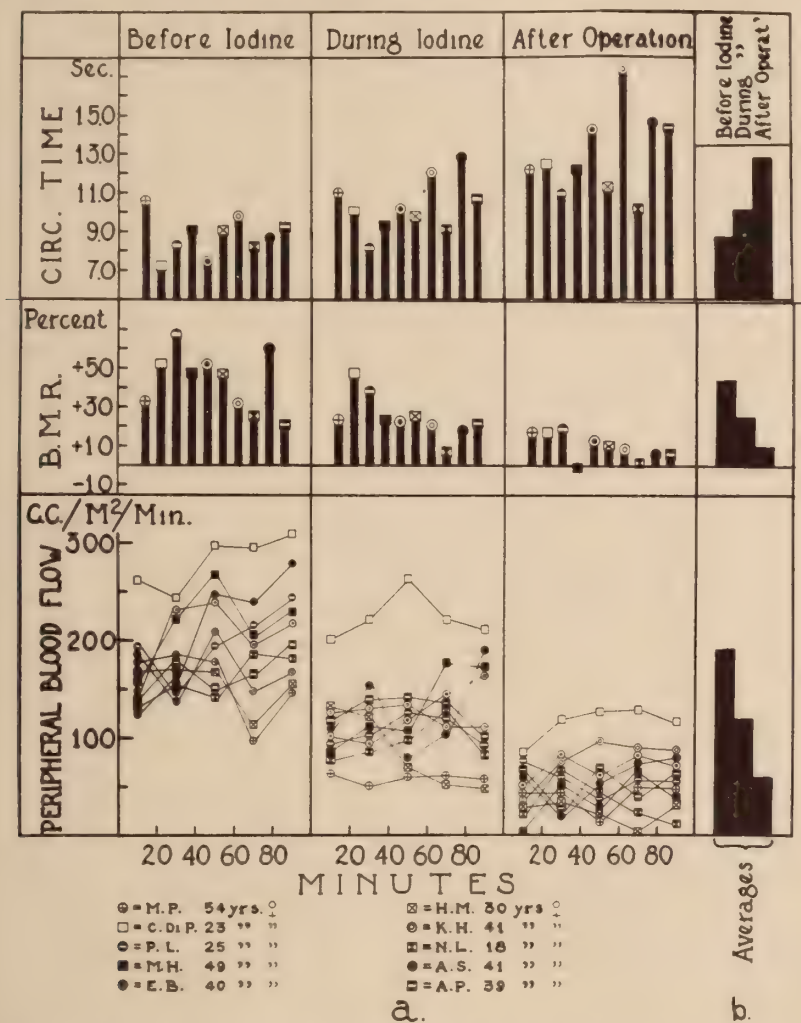


FIG. 1. In Figure 1a are plotted the average peripheral blood flow, basal metabolic rate and circulation time "Before Iodine," "During Iodine" and "After Operation," for each subject. In this figure, as well as in Figure 2, each patient is represented by a symbol. In Figure 1b averages for the whole group are also shown.

Rectal temperature. The rectal temperature showed no significant change (Table 1). The greatest range of temperature in any one patient was plus or minus 0.25°C.

Pulse rate and pulse pressure. The pulse rates in each of the 10 patients and in the group averages showed decreases which ran parallel with changes

in basal metabolic rate and peripheral blood flow. The average pulse pressures showed similar changes (Table 1).

Circulation time. The circulation time was short "Before Iodine". Definite but not striking increases occurred "During Iodine" and again "After Operation" (Table 1) (fig. 1).

DISCUSSION

The trend of peripheral blood flow for each patient followed a similar pattern in the phases "Before Iodine", "During Iodine", and "After Operation". In the initial phase, at a time when the basal metabolic rate was high, the peripheral blood flow was also increased. Observations made during the administration of iodine showed a fall in basal metabolic rate and a parallel decrease in peripheral blood flow. In the latter part of the postoperative period, after subtotal thyroidectomy, further decrease in basal metabolic rate and peripheral blood flow occurred. There was a linear relationship between the level of the basal metabolic rate and the peripheral blood flow since with progressive fall in basal metabolic rate there was fall in peripheral blood flow (fig. 2). There was wide scattering of peripheral blood flow at various levels for individual patients during the three phases (fig. 1). This appears to be due in part to different basal metabolic rates and in part to different room temperatures for each patient. These results are in agreement with the observations of Hick, Keeton, Glickman, and Wall (8) and of Hardy and Soderstrom (9) who made a more definite correlation between rise in environmental temperature and increase in the peripheral blood flow. Because of the rôle played by environmental temperature, care was exercised to keep it approximately the same during all observations on any one patient (for example, subject P. L., fig. 3).

The skin of the patients appeared hot and flushed in the initial phase, even though these subjects were under basal conditions. "Before Iodine" the average skin temperature and peripheral blood flow were elevated at a time when the basal metabolic rate was high, and with fall in basal metabolic rate "During Iodine", and again "After Operation" there was a progressive and parallel decrease in average skin temperature and peripheral blood flow.

Analysis of these data revealed no direct correlation between the average skin temperature and the temperature of the hands and feet (Table 1). The hands, however, followed more closely the average skin temperature. Between the first and second phase average skin temperature fell $0.68^{\circ}\text{C}.$, while the temperature of the hands showed an average decrease of essentially the same magnitude ($0.74^{\circ}\text{C}.$). Comparison of the phase "During Iodine" and "After Operation" showed that although the average skin temperature fell $0.50^{\circ}\text{C}.$, the average temperature of the hands decreased only $0.02^{\circ}\text{C}.$ The temperature of the feet, for the most part, underwent more rapid and wider fluctuations in temperature.

An unusual constancy in rectal temperature was present in all patients during the observations. The average skin temperature for the group decreased $1.18^{\circ}\text{C}.$ from the time of the first observations until after subtotal thyroidectomy. The rectal temperature, on the other hand, only fell $0.06^{\circ}\text{C}.$ This emphasizes a point made in the preceding paper (6), namely, that skin temperature was the more important in the estimation of heat storage and peripheral blood flow, since it changes more in short periods of time.

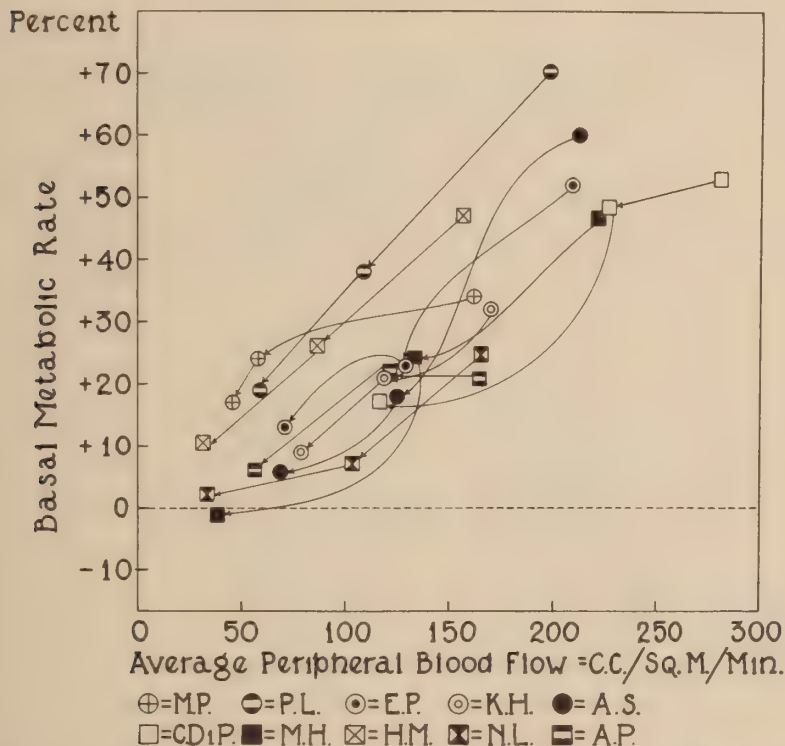


FIG. 2. In this figure the data for peripheral blood flow are plotted against corresponding basal metabolic rates. A linear relationship is established, since with fall in basal metabolic rate the peripheral blood flow also decreased.

The cardiac output was measured in one patient, A. S., in order to correlate it with peripheral blood flow. Because each of the procedures requires most of a morning, the cardiac output was measured under basal conditions on the day following studies of peripheral blood flow. It was estimated by the acetylene method (10, 11). In the phase "Before Iodine", when the basal metabolic rate was plus 60 per cent and the peripheral blood flow 212 cc. sq.m. min., the cardiac output measured 3.48 liters sq.m. - min. "During Iodine", after the basal metabolic rate and peripheral blood flow had fallen to plus 18 per cent and 125 cc./sq.m. min. respec-

tively, the cardiac output decreased to 2.53 liters/sq.m./min. "After Operation", when further decrease to a basal metabolic rate of plus 6 per cent and peripheral blood flow of 69 cc./sq.m./min. had occurred, the cardiac output was 2.02 liters/sq.m./min., values which were now all within the normal range (fig. 4). There is marked increase in oxygen re-

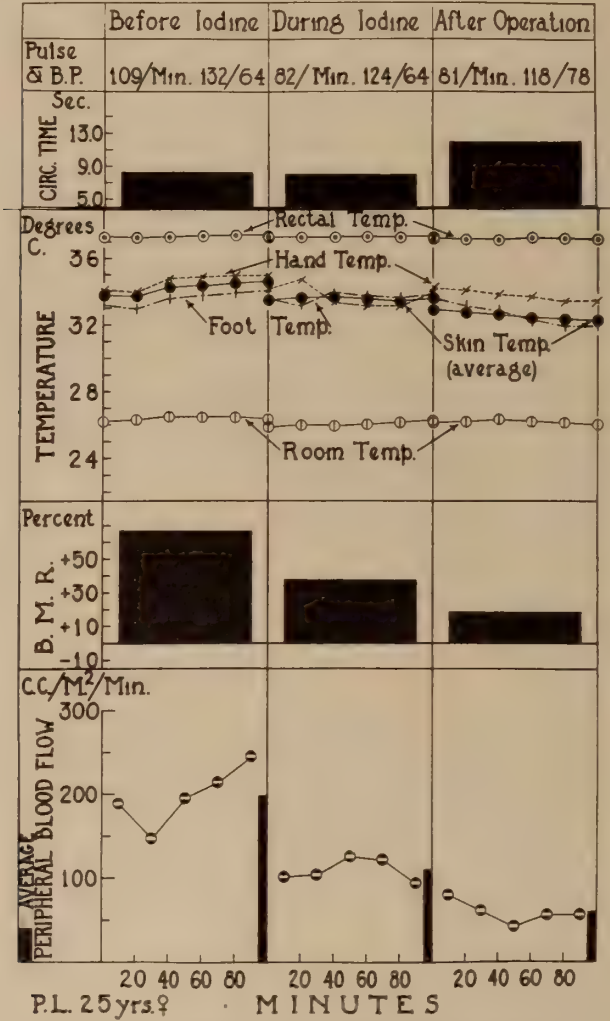
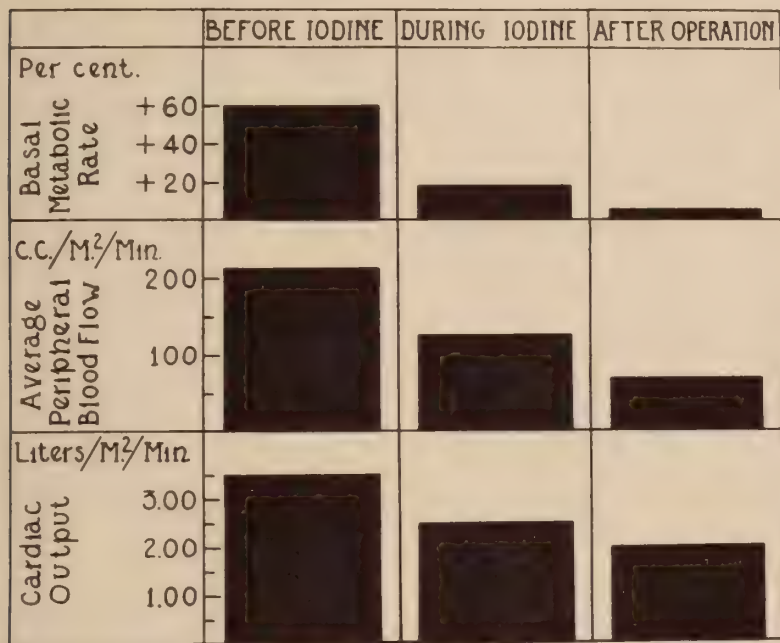


FIG. 3. In this figure are plotted data relating to subject P. L.

quirements in hyperthyroidism. The organism attempts to provide this by increasing the volume output of blood (1). Another compensatory measure may be the increase in circulating blood volume (2). The partition of the cardiac output to the various parts of the body in man is not known. Levy and Blalock (12) have made some approximations in dogs.

In the patient, A.S., in whom the cardiac output was measured, the amount allotted to the periphery was calculated by dividing the peripheral blood flow in cc./sq.m./min. by the cardiac output in cc./sq.m./min. Six per cent of the cardiac output was allotted to the peripheral circulation "Before Iodine". "During Iodine" five per cent of the cardiac output was allocated to the peripheral vascular partition. "After Operation", three per cent only of the cardiac output was distributed to the peripheral circulation. Although the quota of the cardiac output allotted to the periphery during the thyrotoxic phase was double that provided in the last phase, the



A.S. 41yrs. ♀

FIG. 4. In this figure are plotted the average basal metabolic rate, the average peripheral blood flow and the cardiac output in subject A. S. "Before Iodine," "During Iodine" and "After Operation."

total volume output from the heart appeared ample to provide for this increased amount of blood supplied to the periphery.

The circulation time was estimated in order to have an additional objective measurement to correlate with peripheral blood flow. These results demonstrate that in the hyperthyroid state when the basal metabolic rate and peripheral blood flow were elevated, the circulation time was short, that is to say, the velocity of blood flow was increased; with decrease in the former "During Iodine" and again "After Operation" there was progressive increase in circulation time (fig. 1) (Table 1).

Boothby and Rynerson (1) have observed that in hyperthyroidism there is greater increase in cardiac output than occurs in a normal subject as a result of a corresponding increase in oxygen consumption due to work. They have suggested the presence of a special circulatory stimulant to account for this phenomenon. Although the blood volume is increased, and the amount of blood allotted to the periphery increased, the heart increases its output so that the increased volume of circulating blood is kept in motion at a greater velocity of flow. These changes seen in the hyperthyroid state demonstrate and emphasize the strain under which the organism labors in hyperthyroidism. During iodine therapy, with fall in basal metabolic rate, there was decrease in peripheral blood flow and cardiac output, and increase in circulation time. Following subtotal thyroidectomy, however, the further decrease in the peripheral blood flow and cardiac output, and the further increase in the circulation time, demonstrate that operation accomplishes something in the economy of the cardiovascular system which was not achieved by iodine therapy alone.

SUMMARY

Using techniques described in an earlier paper (6), measurements have been made of peripheral blood flow in 10 patients suffering from Graves' disease, "Before Iodine" was given, "During Iodine" therapy, and "After Operation", respectively. In addition, certain other measurements of the circulation were recorded. The results are summarized as follows:

1. In the thyrotoxic phase when the basal metabolic rate was elevated, the peripheral blood flow in cc./M²/min. was increased. Parallel decrease in basal metabolic rate and peripheral blood flow occurred during the administration of iodine and again after subtotal thyroidectomy. A linear relationship was apparent.

2. The circulation time "Before Iodine" was short. "During Iodine" and "After Operation" successive increases in circulation time took place. The changes were of an opposite order to those encountered in basal metabolic rate and peripheral blood flow.

3. Average skin temperature, pulse rate and pulse pressure followed roughly the fall in basal metabolic rate and peripheral blood flow.

4. No direct relationship was observed between average skin temperature and the temperature of the hands and feet. This was particularly true with respect to the feet.

5. No significant changes in rectal temperature were observed.

6. The cardiac output, in the one patient in whom it was measured, showed changes parallel to those in basal metabolic rate and in peripheral blood flow during the three phases.

7. From the therapeutic standpoint, it appears that operation attains something in the economy of the cardiovascular system not achieved by the use of iodine.

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MASSETER AND TEMPORAL MUSCLE TENDERNESS IN SYPHILITIC TRIGEMINAL NEURITIS*

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Muscle tenderness has been frequently observed in peripheral neuritis, yet very little attention has been paid to its occurrence in neuritis affecting the cranial nerves. The muscles innervated by the fifth and seventh cranial nerves are accessible to palpation. Peripheral paralysis of the seventh facial nerve (Bell's Palsy), in my experience, is almost never associated with tenderness in the facial musculature. However, the masseter and temporal muscles which are innervated by the trigeminal nerve are occasionally both painful and tender in cases where there is a neuritis due to syphilis. This condition is by no means a common one. The following cases are examples in which neuritis of the motor branches of the trigeminal nerve was present, and tenderness in the muscles was a constant and diagnostically significant finding.

CASE REPORTS

Case 1. History (Adm. 372300.) A married man, age 24, was admitted to The Mount Sinai Hospital on October 18, 1934 with the chief complaint of pain in the left cheek.

The patient had always been in good health until February 1934, eight months before admission to the hospital, when there developed numbness and tingling in the left cheek following a prolonged exposure of the left side of his face to cold air. Shortly thereafter it was noted that both eyes teared easily, causing his vision to become blurred. In June 1934, the "numbness" in the left cheek recurred and spread to the entire left face. At this time he found he was unable to chew on the left side, and noted an impairment of hearing and occasional pain in the left ear. One month before admission he began to complain of severe shooting pain in the left side of the face. These pains persisted intermittently up to his admission.

Examination. The patient was a well nourished and well developed male, apparently in great pain. He kept his left cheek covered with the hands. There was no evidence of disease of the internal organs. The left masseter and temporal muscles were weak and showed definite atrophy.

On opening the mouth, the jaw deviated to the left. The bite was poor on the left. The muscular contractions palpated over the left masseter and temporal muscles were much weaker than those felt on the right. These muscles were exquisitely tender to deep and light pressures. There was absent sensation for all superficial modalities in the distribution of the lower two divisions of the left trigeminal nerve.

* These cases were admitted to the Neurologic Service of The Mount Sinai Hospital when the author was attending neurologist.

The mucous membranes were also involved. On mimetic innervation, the left nasolabial fold was noted as deeper than the right. There was a slight impairment of hearing on the left side, with bone conduction greater than air conduction. The caloric tests were normal.

Laboratory Data. A lumbar puncture showed an initial pressure of 110 mm. of water; the fluid was clear, contained two lymphocytes and a total protein of 32 mg. per cent. The globulin, colloidal gold and Wassermann tests were negative. The blood Wassermann and Kahn reactions, however, were four plus. The cerebrospinal fluid hydrodynamics were normal.

Course. The patient was placed on antiluetic therapy, and after the first course of treatment he was discharged to his family physician for further care. When the patient was observed in the follow-up clinic three months later, there was great improvement. The masseter and temporal muscle tenderness had disappeared and the atrophy had greatly diminished. On opening the mouth, the jaw deviated only slightly to the left. Except for a slight zone of hypalgesia in the perioral region on the left, sensation had returned to normal. The corneal reflexes were present and equal.

Case 2. History (Adm. 377528.) A widow, aged 54 years, was admitted to The Mount Sinai Hospital on November 17, 1934 with the chief complaints of burning and a bitter taste in the left side of the mouth.

Except for the fact that she was considered to be a "neurotic" individual she was apparently in good health until seven months before admission when she began to complain of a burning and bitter sensation in the left upper part of the mouth. This was persistent. During September 1934 a tooth in that region was extracted, but without relief. In addition to the above symptoms she suffered with severe pain in the left side of the face which had persisted for two weeks. Chewing and biting aggravated this pain. A blood Wassermann test at this time gave a four plus reaction. Since the onset of her illness she had become progressively weak and had lost ten pounds in weight.

Examination. The patient was a chronically ill female who was in acute pain, nursing the left cheek with her hands. Except for a few chronic arthritic changes in the finger joints, the systemic examination was negative. Mentally, she was depressed and extremely hypochondriacal. The only positive findings in the neurological examination were those of the left fifth cranial nerve. There was a definite tenderness of the left masseter and temporalis muscles, even to light pressure. Pain, touch and temperature were diminished in the distribution of the lower two divisions of the left trigeminus; the mucous membranes were involved. There was no deviation of the jaw, nor was there visible atrophy or marked weakness of the masseter and temporalis muscles. The pupils were equal, regular and reacted well to light and in accommodation.

Laboratory Data. The blood Wassermann and Kahn reactions were four plus. The cerebrospinal fluid Wassermann reaction and colloidal gold curve were negative. The cerebrospinal fluid was clear and colorless; contained 12 lymphocytes and total protein of 47 mg. per cent. The globulin was not increased. The initial pressure was 170 mm. of water; and there was no block to jugular compression.

Course. The patient was placed on antiluetic therapy. After she had received six injections of bismuth and six injections of neoarsphenamine the symptoms lessened.

Case 3. History (Adm. 379719). A 33 year old Porto Rican presented himself at the hospital in December 1934 with the chief complaint of pain in the eye and jaw on the right side for two and a half months.

In 1921 he contracted a hard penile chancre. Although he did not receive anti-

luetic treatment at any time, it was claimed that several blood Wassermann tests were reported to be negative. The following year there developed pain in the epigastrium after meals. An x-ray examination of the gastrointestinal tract in 1939 revealed a peptic ulcer. On a Sippy diet the abdominal symptoms disappeared.

The illness for which he was admitted began ten weeks before admission to the hospital with an itching sensation accompanied by pain in the region of the right eye. The following week he noted that the affected eye began to close, and severe headaches in the right temporal region appeared. His jaw began to ache whenever he would chew or open his mouth wide. A very tender area appeared over the right cheek which was very painful to touch. All symptoms progressed. The headaches became generalized and radiated to the occiput. The pain was aggravated on head movement. During the two months before admission he had suffered with intermittent pain and buzzing in the right ear. He vomited sporadically.

Examination. The patient was a well nourished, well developed male, lying in bed, apparently experiencing acute pain, in the region of the right eye; the conjunctiva of the right eye were congested, and the lids edematous; the right ear drum was hyperemic; there was tenderness to moderate pressure over the right mastoid region.

The neurological examination showed: deep reflexes which were depressed; the left ankle jerk was absent; there were bilateral equivocal Babinski signs and absent abdominal reflexes. There was impairment of sensation for all superficial modalities in the entire distribution of the right trigeminal nerve; the mucous membranes and to a lesser degree the adjacent second cervical dermatome were also involved. Taste was slightly impaired on the right side of the tongue. On opening the mouth the jaw deviated to the right. There was weakness but no visible atrophy of the right masseter and temporalis muscles. These muscles were exquisitely tender to deep and light pressures. The right pupil reacted sluggishly to light. There was a slight ptosis of the right upper eyelid and a questionable, significant external rectus weakness on the same side. Photophobia was very prominent in the affected eye. There was a slight hearing impairment of the mixed type on the right.

Laboratory Data. The blood Wassermann and Kahn reactions were four plus. A lumbar puncture showed clear cerebrospinal fluid under an initial pressure of 160 mm. of water, with 555 lymphocytes per cu. mm. There was no block to jugular compression. The globulin was positive. The Wassermann reaction was four plus. The colloidal gold curve was 5555420000. An x-ray examination of the sinuses and of the petrous ridge was negative.

Course. The patient was placed on antiluetic therapy with bismuth and made a progressive improvement. When he was discharged from the hospital forty-six days after admission, the tenderness of the masseter and temporal muscles had disappeared, the sensory changes had become less marked, and examination of the cerebrospinal fluid showed only four cells.

Case 4. History (Adm. 421123). A 48 year old housewife entered the hospital on March 8, 1938 with the chief complaints of pain in the left face and drooping of the left eyelid. In September 1937 she noted transient blurred vision in the left eye and sharp shooting pains behind the left eyeball. In November 1937 the shooting pains recurred and spread to involve the supraorbital, malar, aural and entire facial region on the left side. Three weeks before admission the left superior eyelid began to droop and two weeks later the left masseter became tender to touch.

Examination. There was no evidence of disease of the thoracic or abdominal viscera. Neurologically the findings were limited chiefly to the left third, fourth and fifth cranial nerves. There was a left internal and complete external ophthalmoplegia. The right pupil was slightly irregular and reacted sluggishly to light. On opening the mouth the jaw deviated to the left; the bite was weak on the left. The

left temporalis and masseter muscles were markedly tender to pressure. There was percussion tenderness over the left temple and malar regions. There was complete loss of sensation for pain, temperature and touch involving the skin and mucous membranes in the distribution of the left trigeminus. The left corneal reflex was absent.

Laboratory Data. The pertinent laboratory findings were the four plus blood Wassermann and Kahn reactions. The cerebrospinal fluid was clear and colorless and under an initial pressure of 320 mm. of water; it contained 9 monocytes and a total protein of 78 mg. per cent. The cerebrospinal fluid Wassermann reaction was four plus and the colloidal gold curve was 01111222222.

Course. The patient was placed on antiluetic therapy and showed an improvement in signs and symptoms. At the end of three weeks of treatment the Wassermann reaction of the cerebrospinal fluid became negative while that of the blood remained positive.

COMMENT

The constant symptom in these patients with trigeminal neuritis was tenderness of the masseter and temporal muscles. It was of the type elicited in muscles affected by peripheral neuritis. The pathophysiologic explanation for the tenderness of muscles in trigeminal neuritis is probably the same as that for peripheral neuritis. Another significant fact was that in all these cases syphilis was the etiologic agent. This was proven not only by the serologic studies but by the results of the antiluetic therapy. Whether the pathologic change in the trigeminus was an interstitial neuritis or a perineuritis is immaterial. Either or both conditions may exist in patients with luetic basilar meningitis.

The tenderness of the masseter and temporal muscles may presumably occur in any inflammation of the trigeminus but non-syphilitic inflammations localized to the fifth cranial nerve are rare, hence these signs are not frequently noted. In herpes zoster of the trigeminus the motor division is rarely affected. Occasionally masseter pain has been observed in infiltrating tumor of the fifth cranial nerve but this is rarely severe.

SUMMARY

Four cases are described in which exquisite tenderness of the masseter and temporal muscles was found in patients suffering with luetic trigeminal neuritis. The muscle tenderness and other signs of involvement of the fifth nerve disappeared with antiluetic therapy. The presence of such muscle tenderness is strongly in favor of the diagnosis of syphilitic inflammation of the trigeminal nerve.

I could find no mention of this symptom in the medical literature available to me.

THE ROENTGENKYMogram IN MYOCARDIAL INFARCTION

III. CASES WITH NORMAL ELECTROCARDIOGRAM

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In 200 cases of recent and old myocardial infarction due to coronary occlusion, roentgenkymographic examination revealed distinct abnormalities in left ventricular pulsation in 75 per cent (1, 2). These abnormalities consisted of 1) complete or partial systolic expansion (paradoxical pulsation) and 2) localized diminution or absence of pulsation. It was also pointed out that abnormal ventricular pulsations were observed in a number of cases in which the electrocardiogram returned to normal or nearly normal. The diagnostic importance of the roentgenkymogram in these cases was emphasized. A more detailed analysis of the clinical, electrocardiographic and roentgenkymographic features of 18 such cases is presented in this report, forming 9 per cent of the entire series of 200 cases.

In table I, 36 cases (18 per cent of the entire series) in which the electrocardiogram returned to normal or near normal are grouped according to their roentgenkymographic findings. These findings were considered to suggest the presence of myocardial infarction when there was systolic expansion or marked diminution in pulsation. When the diminution in pulsation was slight to moderate, the findings were considered inconclusive. Nine cases are included in which the electrocardiogram returned to normal except for a persistence of small Q waves; these electrocardiograms were classified as slightly abnormal. It is seen in this table that an abnormal roentgenkymogram was obtained in 22 of the 36 cases, i.e., 61 ± 8 per cent. In the remaining 164 cases of coronary occlusion in which the electrocardiographic alterations persisted throughout the clinical course, abnormal pulsations suggestive of myocardial infarction were found in 77 ± 3 per cent. The slight difference can be accounted for by the fact that the cases in which the electrocardiogram returned to normal were apt to be less severe.

A detailed analysis of the clinical, electrocardiographic and roentgenkymographic findings in the 18 cases in which the electrocardiogram returned entirely to normal with persistent abnormal pulsations, is presented in table II. In table III these data are summarized. As a rule, the acute attack was mild or only moderately severe. There was no heart failure nor cardiac enlargement during and after the attack, angina pectoris was absent or mild and functional recovery was good. Hence in the majority

of these 18 cases (9 per cent of the entire series of 200 cases) the abnormal roentgenkymographic findings were the only objective signs of previous coronary occlusion with infarction or indeed of any organic heart disease. This emphasizes the diagnostic value of roentgenkymography in patients with symptoms pointing to coronary artery disease or occlusion when the electrocardiogram is completely normal.

Analysis of the electrocardiograms taken during the acute attack revealed that the pattern of anterior infarction was present in 8 cases, posterior infarction in 3, both anterior and posterior infarction in 3 and unclassified in 3. In one case the electrocardiogram remained normal throughout the course of the disease including the acute stage. The electrocardiographic pattern became normal within one month or less in 3 cases, six months or less in 5, one to two years in 8 and three years in 1

TABLE I

The roentgenkymogram in 36 cases of previous coronary occlusion with normal or slightly abnormal electrocardiogram

	NO. OF CASES	ROENTGEN- KYMোগRAM		INCON- CLUSIVE
		Ab- normal	Normal	
Group 1. Electrocardiogram normal during entire course.....	1	1	0	0
Group 2. Electrocardiogram abnormal in acute stage, becoming normal within 6 weeks.....	5	3	1	1
Group 3. Electrocardiogram remaining abnormal beyond 6 weeks:				
A. Finally becoming normal.....	21	14	7	0
B. Remaining slightly abnormal.....	9	4	4	1
Total.....	36	22	12	2

case. Electrocardiographic abnormalities generally consisted of RS-T deviations and T wave inversions which progressed to normal in serial records. In 5 cases deep Q waves in leads 1, 3 or 4 disappeared following recovery: as a rule, this abnormality is permanent.

The roentgenkymogram revealed partial or complete expansion in 13 cases and marked localized diminution or complete absence of ventricular pulsation in 5 cases. As a rule the abnormalities remained unchanged despite the complete return to normal of the electrocardiogram but in 2 cases partial systolic expansion was replaced by a markedly diminished pulsation of normal wave form. In one exceptional case the roentgenkymogram became abnormal after the electrocardiogram had returned to normal.

The above analysis indicates that healing of myocardial infarction may

TABLE II

Detailed analysis of 18 cases of previous coronary occlusion with normal electrocardiogram and abnormal roentgenkymogram

GROUP	CASE	ADMIS- SION NUM- BER	AGE	SEX	DATES OF INFARCT			CLINICAL STATE DURING OBSERVED ATTACK			SUBSEQUENT COURSE				HYPERTENSION		ELECTROCARDIOGRAM			ROENTGENKYOGRAM		
					First observed attack	Previous attack	Subsequent at- tack	Severity	Heart failure	Cardiac enlarge- ment	Functional capacity	Angina pectoris	Heart failure	Date	Findings	Location	Date	Findings				
1	1. I. S.	456551	55	M	12/37	0	0	Mild	0	+	Moderately restricted	++	0	++	0	++	12/37 1/38 11/38 6/41	Normal Normal Normal Normal	?	12/37 1/38 11/38 6/41	Systolic expansion Same Same Same (fluoroscopy)	
2	2. W. B.	419474	52	M	1/38	0	0	Mild	0	0	Unrestricted	0	0	0	0	0	1/38 2/38 10/38 2/41	T ₁ , 4 deeply inverted Normal Normal Normal	Anterior	1/38 2/38 10/38 2/41	Systolic expansion and diminution Same Marked diminution and irregularities Marked diminution and irregularities	
	3. J. K.	404312	55	M	2/37	0	0	Mild	0	0	Unrestricted	0	0	0	0	0	2/ 6/37 2/20/37 5/38	Deep Q ₁ , R T ₁ slightly elevated Normal Normal	Atypical anterior	5/38 6/41	Systolic expansion Same	
	4. A. L.	424313	44	M	4/38	0		Mild	0	0	Slightly re- stricted	0	0	0	0	0	4/ 4/38 4/11/38 4/21/38	T ₁ semi-inverted Same Normal	Anterior	4/11/38 4/21/38	Marked diminution Slight systolic ex- pansion	
							5/38	Severe	+	0	Markedly re- stricted	++	0	++	0	0	6/38 7/38 11/39	Deep Q ₁ , T ₁ , 2, 4 in- verted Same Same	Anterior	6/38 7/38 11/39	Marked diminution with irregularities Absent pulsation Same	
3	5. C. B.	411390	44	F	4/14/37	3/37		Severe	++	+	Moderately restricted	+	0	+	0	+	4/37 7/37 12/38	R T ₁ , 2, 4 depressed T ₁ , 2, 4 inverted T ₁ , 2, 3, 4 diphasic Normal	Anterior		12/38	Diminution with ir-

6. T. B.	410877	50	M	7/37	0	0	Mild	+	0	Slightly re- stricted	+	0	0	7/37 12/38	RT ₁ , 2 depressed T ₁ , 3, inverted Normal	Anterior	12/38	Absent pulsation
7. J. B.	409353	37	M	5/37	0	0	Moderate	+	0	Unrestricted	slight	0	+	5/37 9/37 1/38	Small Q ₁ , 2; T ₁ , 2 deeply inverted Small Q ₁ ; T ₁ inverted Normal-small Q ₂ , slightly inverted T ₃ Same Same	Posterior	9/37 1/38 3/39 3/40	Systolic expansion Same Same Same (fluoroscopy)
8. I. E.	395766	53	M	7/36	0	0	Moderate	0	0	Moderately restricted	++	0	++	7/36 7/38 12/38	T ₂ , 3 inverted Normal Normal	Posterior	7/38 12/38	Systolic expansion Same
9. L. C.	405109	46	M	3/37	0	0	Mild	0	0	Unrestricted	0	0	0	3/37 10/38	T ₁ , 2, inverted Normal	Anterior	10/38	Diminution
10. M. H.	472403	50	F	2/39	0	0	Moderate	0	+	Moderately restricted	++	0	+	2/39 4/39	Deep Q ₁ , T ₁ , 2, in- verted and coved Normal	Anterior	4/39	Partial systolic ex- pansion and marked diminution
11. M. K.	382364	51	M	7/35	0	0	Moderate	+	+	Slightly re- stricted	slight	0	0	7/35 4/38 4/39 4/41	Deep Q ₁ , RT ₁ , 2, 3 elevated; T ₁ , 2, 3, 4 inverted Normal Normal Normal	Anterior - posterior	4/38 4/39 4/41	Systolic expansion Same Same (fluoroscopy)
12. D. P.	430407	60	F	10/38	0	0	Moderate	+	+	Slightly re- stricted	+	0	++	10/38 3/39 1/41	T ₁ , 4 inverted Normal Normal	Anterior	10/20/38 3/39 1/41	Slight diminution Marked diminution, probable systolic ex- pansion Systolic expansion
13. H. S.	422369	53	M	4/38	0		Mild	0	0	Unrestricted	0	0	0	4/38 6/38 3/40	T ₁ , 4 inverted Same Normal	Anterior	4/38 6/38 3/40	Absent pulsation Same Diminution

TABLE II—Concluded

GROUP	CASE	ADMIS- SION NUM- BER	AGE	SEX	DATES OF INFARCT			CLINICAL STATE DURING OBSERVED ATTACK			SUBSEQUENT COURSE			HYPERTENSION	ELECTROCARDIOGRAM			ROENTGENKYOGRAM			
					First observed attack	Previous attack	Subsequent at- tack	Severity	Heart failure	Cardiac enlarge- ment	Functional capacity	Angina pectoris	Heart failure		Date	Findings	Location	Date	Findings		
14. J. S.	387855	50	F		12/35	0	0	Moderate	+	+		Slightly re- stricted	+	0	+	12/35	T _{3, 4} inverted	Atypical- posterior	11/37	Normal	Partial systolic ex- pansion Same
15. B. S.	394181	58	F		6/36	0		Moderate	0			Slightly re- stricted	+	0	0	6/36	Deep Q _{1, 3} ; RT _{1, 2, 3} elevated, T _{1, 2, 3, 4} inverted	Anterior- posterior	12/37	Normal	Systolic expansion
16. A. V.	441778	66	M		6/39	0	0	Moderate	++	0		Unrestricted	0	0	+	6/39	Deep Q _{2, 3} ; RT _{2, 3} elevated, T _{2, 3} in- verted	Posterior			Diminution and de- layed systole
17. A. L.	388628	59	M		1/36	0		Moderate	+	0		Mildly re- stricted	+	0	0	1/36	Sm all Q ₂ and R ₄ , T ₃ inverted	Atypical posterior			
18. M. W.	418965	56	M		1/38	0	0	Moderate	0	+		Unrestricted	0	0	0	1/38	T _{1, 2, 3} inverted, T ₄ low	Anterior- posterior	10/38	Normal	Systolic expansion
																7/38	Normal		7/38	Normal	Marked diminution
																12/38	T _{2, 3} slightly inverted		12/38	T _{2, 3} slightly inverted	Systolic expansion
																4/41			4/41		Same (fluoroscopy)

TABLE III

Summary of clinical findings in eighteen cases of coronary occlusion with normal electrocardiograms and abnormal roentgenkymograms

Sex distribution	2.5 males to 1 female
Average age	52 years
Patient came under observation during initial attack in	17 cases
Subsequent attacks in	5 cases
Severity of observed attack	Mild 7
	Moderate 10
	Severe 1
	None 10
Heart failure during attack	Mild 6
	Moderate 2
	Slight 6
Cardiac enlargement	None 12
Subsequent course (1-6 years):	
Functional capacity	No or slight restriction 13
	Moderately restricted 5
Heart failure	None
	Mild 5
Hypertension	Moderate 2
	None 11

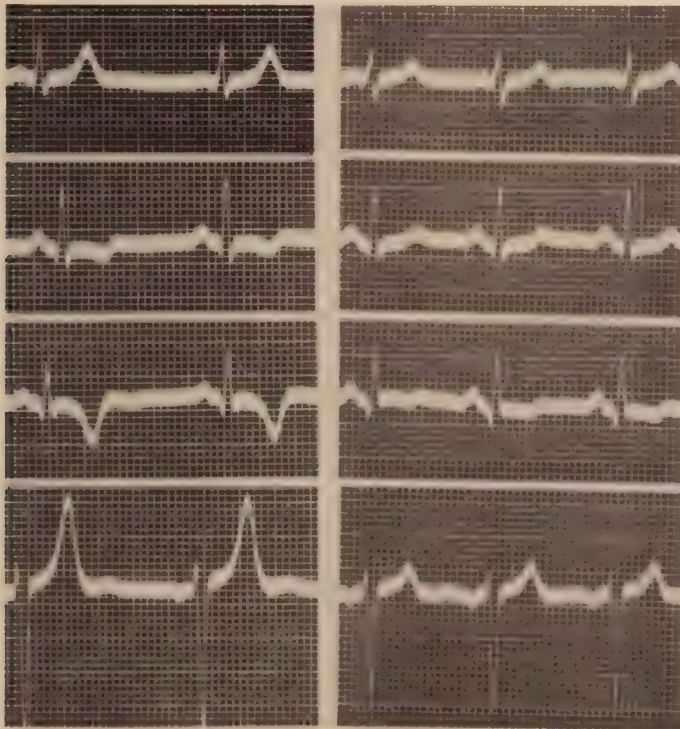


FIG. 1. Case 7. Male, aged 37. Acute coronary occlusion May, 1937.

A. Electrocardiogram during acute stage shows small Q_2 and Q_3 , deeply inverted T_2 and T_3 and tall, pointed T_4 , findings characteristic of recent infarction of the posterior surface of the left ventricle.

B. January 1938. T_2 and T_4 have become normal. T_3 is slightly inverted and a small Q_3 remains, but these findings are not abnormal.

be accompanied by complete restoration of conduction even though myocardial contraction remains impaired. However, the latter need not



FIG. 2. Case 7. Roentgenkymogram taken January 1938, reveals complete systolic expansion (paradoxical pulsation) of the lower $\frac{2}{3}$ of the left ventricular border. As the aorta expands and the normal upper $\frac{1}{3}$ of the left ventricle contracts during systole the abnormal lower $\frac{2}{3}$ shows a lateral movement. This is characteristic of myocardial infarction. Record taken May, 1937 is not shown since the findings were identical.

result in functional impairment since the majority of patients became symptom-free with no limitation of their capacity for activity.

CONCLUSIONS

A detailed analysis is presented of 18 cases of coronary occlusion in which the electrocardiogram returned to normal but abnormal ventricular contraction, demonstrated roentgenkymographically, persisted. This indicates the importance of the latter examination in cases in which symptoms of coronary disease or occlusion are present but other objective confirmation is lacking.

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THE NEUROLOGICAL MANIFESTATIONS OF PERIARTERITIS NODOSA

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A frequent clinical feature of periarteritis nodosa is the presence of peripheral or central nervous system disturbances. In recent years more instances of periarteritis nodosa have been recognized and, therefore, a large literature has accumulated on the subject. Most of the reports have been made by pathologists and internists but, though the neurological complications have been stressed, little attention has been paid to the nature of the signs and symptoms. A comprehensive and excellent description of periarteritis nodosa with its protean and bizarre manifestations has been recently made by Rose Spiegel. Her material was based on fifteen case histories of patients with verified periarteritis nodosa observed at The Mount Sinai Hospital from 1919 to 1934. Eight of these patients had neurological complications. Since then nine more proven cases have been studied in this hospital and, of these, seven had symptoms and signs of disease of the nervous system. The present communication deals chiefly with the hospital records for the last seven years.

CASE REPORT

Case 1.¹ History (Adm. 414842). A 52 year old housewife was admitted to the service of Dr. B. S. Oppenheimer on October 3, 1937 complaining of pains in the joints. For one year she had had shooting pains in the feet and ankles. At the menstrual period the feet became red, swollen and "burned." For the five months preceding admission she had been treated for arthritis. She also complained of palpitation, dependent edema, weakness and dyspnea on exertion. Five weeks before admission she had had diarrhea and a sudden appearance of pruritic discrete eruption of both thighs. For one week fever, malaise and high blood pressure had been noted.

Examination. The patient was a moderately obese woman lying apathetically in bed. The pupils were irregular. The optic nerve heads were blurred and there were scattered hemorrhages throughout both fundi. The heart was enlarged to the left. A systolic murmur was heard at the apex. The blood pressure was 190 systolic and 120 diastolic. A few moist râles were heard at the right base. Several scattered hemorrhagic and erythematous macules with central excoriations were found on the thighs and arms. The reflexes were active and equal.

Laboratory data. Hemoglobin, 58 per cent; red blood cells, 3,300,000; white blood cells, 7,350; segmented polymorphonuclear leucocytes 72 per cent; non-segmented polymorphonuclear leucocytes, 14 per cent; monocytes, 4 per cent; lymphocytes, 10 per cent; polychromatophilia, anisocytosis and poikilocytosis. The urine showed

¹ This case was reported by Dr. Moscheowitz.

two plus albumin, a few white blood cells, many red blood cells, cellular hyaline and granular casts; the specific gravity was 1020. The value for blood urea nitrogen was 26 mg. per cent, and on one occasion 40 mg. per cent. X-ray examination of the chest showed enlargement of the heart to the left.

Course. The patient was apathetic but complained of headache. Three days after admission a lumbar puncture revealed uniformly bloody cerebrospinal fluid which did not clot, and was xanthochromic in the supernatant portions. The initial pressure was 190 mm. of water. The fluid contained a total protein of 42 mg. per cent. Subsequent repeated lumbar punctures showed gradual absorption of the blood. A biopsy from the right deltoid muscle on October 8, 1937 revealed necrotizing arteritis and periarteritis. Four days later the patient developed weakness of the left hand and forearm. Neurological examination disclosed signs of meningeal irritation and a left radial nerve palsy. There was a wrist drop, diminished radial periosteal reflexes and decreased sensation for all modalities in the distribution of the radial nerve of the left hand. On October 21 the weakness and wrist drop in the left hand receded. This improvement progressed. Throughout her stay in the hospital she had fever of 100 to 100.5°F., but on October 30 the temperature began to rise and she became progressively drowsy and dehydrated. The urinary findings indicated further kidney damage but there was no clinical evidence of uremia. Some of the observers felt that the progressive drowsiness without the clinical evidence of uremia was of cerebral origin. On November 8, the lumbar puncture showed clear cerebrospinal fluid under a pressure of 80 mm. of water, which contained total protein of 35 mg. per cent. She died on November 9, 1937. An autopsy was not obtained.

Comment. This is a typical instance of single nerve palsy. Such palsies usually regress. The occurrence of gross subarachnoid hemorrhage in this case of periarteritis nodosa is stressed because of its rarity.

Case 2. History (Adm. 475904). A sixteen year old schoolgirl was admitted on February 5, 1940 to the service of Dr. B. S. Oppenheimer with a history of attacks of bronchitis and sinusitis of two years' duration. Six weeks before admission she had had symptoms of polyarthritides, multiple purpuric lesions and abdominal pain.

Examination. Discrete nodules were found in the cervical, axillary and inguinal regions, a loud systolic murmur at the apex, purpuric spots on the heels, soles and elbows, and occasional spots on the hands. The blood pressure was 120 systolic and 88 diastolic. The hemoglobin, 92 per cent; red blood cells, 4,900,000; white blood cells, 21,200, with segmented polymorphonuclear leucocytes 19 per cent; eosinophiles, 66 per cent, basophiles, 1 per cent, lymphocytes 13 per cent, monocytes 1 per cent. The sedimentation rate was 50 minutes. The urine was negative. A biopsy of the skin and muscle in the left deltoid region revealed no significant changes.

Course. Repeated blood counts showed marked eosinophilia up to 75 per cent. The temperature remained normal. The urine concentration power was impaired. The purpuric spots and joint manifestations subsided. The sedimentation rate, however, increased. Otherwise the course was stationary. On February 29, 1940, the patient was discharged from the hospital and observed in the follow-up clinic. On May 31, 1940, she was readmitted because of swelling and pains in the feet and ankles, purpuric spots, swelling of the left eyelids and intermittent vomiting. Examination revealed nodules in the right parietal scalp, enlargement of the heart to the left, purpuric lesion on the dorsum of the feet, the blood pressure was 160 systolic and 100 diastolic in each arm. The laboratory data were practically the same as on the first admission. She continued to complain of abdominal pain. The hypertension increased. On June 9, 1940, she complained of pain in the left little finger and on the next day she had weakness of the right hand. Neurological status at this time disclosed a tremor of the left hand, absent left biceps reflex, weakness of the right

third and fourth fingers, and diminished sensation in the distribution of the right median nerve. She had signs of a right median nerve palsy. The fundus vessels were full and tortuous, and the nasal edges were blurred. Examination of the nose and throat revealed diseased sinuses and tonsils. Tonsillectomy was performed and on histologic examination necrotizing arteritis and periarteritis were found. The tonsillectomy was followed by bilateral sphenoidectomy and repeated irrigations of the sinuses. After the first operation definite clinical improvement occurred. The urine concentration power increased and the white blood count of 35,000 dropped to 7,000. The eosinophilia of 60 per cent decreased to 2 per cent. The blood pressure level diminished to 150 systolic and 90 diastolic. The patient gained weight and she was discharged as in a remission. She is still under observation in the follow-up clinic. The right median nerve palsy has practically disappeared.

Comment. This is another example of an isolated peripheral nerve paralysis. Here again there was relatively quick recovery from the palsy.

Case 3. History (Adm. 381097). A 51 year old carpenter was admitted on June 17, 1935 to the service of Dr. B. S. Oppenheimer because of joint and muscle pains. Since 1928 when his "blood pressure was 200," he had had repeated attacks of hemoptysis because of bronchial telangiectasia. Three months before admission there developed migratory muscle and joint pains. In addition he had sharp shooting pains in the lower extremities which were associated with "heaviness" in the legs.

Examination. The patient was a chronically ill man with incipient cataracts. The heart was enlarged to the left and the peripheral vessels were sclerosed. The blood pressure was 132 systolic and 90 diastolic. There was definite pressure tenderness of the thigh and calf muscles. The positive neurological signs were: absent ankle jerks, depressed left knee jerk, absent abdominal and cremasteric reflexes, diminished sensation for all modalities in both feet, so-called "stocking" distribution, impaired position sense in the toes, loss of vibration sense below the knees. There was slight hypalgesia in the distribution of the left ulnar nerve, which became more pronounced later in the course of the disease.

Laboratory data. White blood cells, 19,000, many of which had toxic granules; polymorphonuclear neutrophils 66 per cent, immature polymorphonuclear neutrophils 27 per cent, and lymphocytes 27 per cent. Urinalysis gave negative results. The cerebrospinal fluid was under pressure of 50 mm. of water, contained a total protein of 35 mg. per cent, no cells, and gave a positive tryptophane reaction. The serology was negative. An x-ray examination of the chest revealed an enlarged left heart and dilated aorta. There was no eosinophilia.

Course. This was characterized by a low grade fever ranging between 100 to 101°F., and generalized aches. Because of the asymmetrical neurological signs periarteritis nodosa was suspected. Later in the illness the patient became cachectic. Atrophy of the interossei and calf muscles became prominent and edema of the legs appeared. The patient became progressively worse and died on July 15, 1935.

Necropsy findings (limited to an abdominal incision). There was extensive periarteritis nodosa involving the vessels of the abdominal and thoracic viscerae. Examination of the sciatic and obturator nerves showed several blood vessels with necrosis of the intimal and muscle layers, cellular infiltration and increased fibrous tissues of the adventitia. The rest of the necropsy disclosed pulmonary tuberculosis, bronchopneumonia, rheumatic mitral and aortic endocarditis, and hypertrophy of all the cardiac chambers.

Comment. This patient had an asymmetrical polyneuropathy. In the lower extremities the involvement was symmetrical and most marked distally, signs usually observed in avitaminosis or toxic neuropathy. In addition, however, there was a

left ulnar palsy which altered the symmetry and character of the peripheral nerve involvement.

Case 4. History (Adm. 475714). A 28 year old housewife was admitted to the Neurological Service on July 2, 1941 because of pains in the extremities. Five weeks before admission the patient noted occasional numb sensations and a dull ache in the sole of the right foot. After a few days she felt moderately severe pain in the right leg and back of the thigh. She also had weakness in the right leg and some pain in the left calf. Three weeks before admission the pain in the right extremity became more severe and the numbness spread to involve the entire right foot. For three days she felt numbness in the left foot. She also complained of fleeting pains in her wrists and shoulders, with the transient appearance of small nodules in her finger tips, mainly of the right hand, which were red and itched. There had been some diarrhea with abdominal cramps for four days.

Examination. The patient was a thin, white woman, lying listlessly in bed and appearing chronically ill. The temperature was 101°F. Except for an occasional musical r le and pulsus trigemini there was no evidence of disease of the abdominal or thoracic viscerae. The blood pressure was 120 systolic and 80 diastolic. The fingers showed slightly tender and pearly nodules. There were several vesicular and hemorrhagic inflammatory lesions on the hands and feet. The neurological status revealed an abnormal gait with a tendency to drag the right leg, an absent ankle jerk on the right, a depressed ankle jerk on the left, weakness of extension and flexion of the right foot, tenderness of the calf muscles on the right, and absent pain, touch, and temperature sensation on the sole of the right foot. These were signs of tibial and peroneal nerve involvement.

Laboratory data. Hemoglobin, 82 per cent; white blood cells 10,000; polymorphonuclear leucocytes, 86 per cent; lymphocytes, 10 per cent; monocytes, 2 per cent; eosinophiles, 2 per cent. The urine was normal. Lumbar puncture showed clear cerebrospinal fluid under a pressure of 120 mm. of water, which contained a total protein of 25 mg. per cent and no cells.

Course. As the disease evolved, daily bouts of fever appeared and the spleen became tender. Subsequent blood counts revealed anemia, hemoglobin 52 per cent and eosinophilia of 26 per cent. There were traces of albumin and occasional red blood cells in the urine. Later urticarial eruptions appeared. All these findings seemed to fit into the diagnosis of periarteritis nodosa. A biopsy of the right calf muscle failed to show a vascular lesion. On July 23, 1941 the patient was transferred to the Medical Service. At this time she complained of numbness in the distribution of the left ulnar nerve. Neurological examination now revealed left ulnar nerve palsy in addition to right tibialis and peroneal nerve lesions. On August 13, 1941, herpes labialis appeared. One week later she complained of blurred vision and diplopia on looking to the left: this was probably due to a left abducens paresis because examination on the next day (August 21) revealed no ocular muscle weakness and there was no diplopia. On August 22 she had two convulsions and on the following day the blood pressure was found to be 150 systolic and 116 diastolic. A lumbar puncture showed clear cerebrospinal fluid which contained 125 red blood cells. On August 25 she had a stiff neck and a bilateral Kernig sign was present. She felt happy but sleepy. On August 28, a left radial nerve palsy with wrist drop appeared. The patient became progressively worse and died on September 4, 1941.

Necropsy findings. There was evidence of periarteritis nodosa of the vessels of most of the organs examined. The sciatic nerve was studied. The brain and spinal cord were not examined.

Comment. In this case there were multiple peripheral nerve palsies, periodically involving single nerve trunks without any symmetry. (Right tibial and peroneal, left ulnar and radial). The abducens weakness was an example of cranial nerve

palsy. The convulsive seizures and stiff neck were manifestations of central nervous system lesions either due to periarteritis nodosa or to secondary hypertensive encephalopathy.

Case 5. History (Adm. 381839). A 34 year old nurse was admitted to the Neurological Service on July 5, 1935 with the chief complaint of numbness of the feet of eight months' duration. Previously she had been studied in many hospitals but no definite diagnosis was made. In 1930 she had a slight peripheral facial palsy. In January of 1934 the patient developed a dry cough which lasted for five months. Eight months before admission she had numbness of the toes, which spread to the feet and later was associated with swelling of the ankles. Three months before admission she had fever and occasional vomiting. During the two months prior to entrance to the hospital there was numbness on the ulnar aspect of the left wrist. She had lost 36 pounds in weight.

Examination. The patient was a tall, poorly nourished white woman who appeared to be chronically ill. There was no evidence of disease of the internal organs. The neurological status disclosed absent ankle jerks and knee jerks, absent abdominal reflexes, diminished sensation for pain, touch, and temperature in both feet and in the left ulnar region, loss of vibration sense in the feet, impaired position sense in the toes, and unequal and irregular pupils which were fixed to light but reacted in accommodation. There was an old right Bell's palsy.

Laboratory data. Hemoglobin, 68 per cent; red blood cells, 4,210,000; white blood cells, 11,700; non-segmented polymorphonuclear leucocytes, 15 per cent, segmented, 71 per cent; lymphocytes, 11 per cent, monocytes, 3 per cent and negative urinalysis. Lumbar puncture yielded clear cerebrospinal fluid under a pressure of 50 mm. of water. The cerebrospinal fluid contained a total protein of 35 mg. per cent. The blood and cerebrospinal fluid Wassermann tests gave negative results.

Course. The course was characterized by remissions. The signs of peripheral nerve lesion diminished and increased. The temperature ranged between 100 and 101°F. On July 21, 1935 she complained of numbness and an "unnatural" feeling in the face, tongue and scalp; the lips felt as if they were burned and swollen. There was objective hypalgesia over the face and mucous membranes of the throat. She complained of headache and fleeting backache. She had attacks of vertigo and on several occasions she vomited. She was depressed and she cried frequently. In general, however, she felt improved and was discharged from the hospital. Subsequently it was learned that the patient died one year later in a Boston hospital where an abdominal operation and, sometime later, post-mortem examination disclosed periarteritis nodosa of the vessels in most parts of the body. Examination of the spinal cord, sciatic and obturator nerves disclosed lesions of periarteritis nodosa.

Comment. This patient had an asymmetrical polyneuropathy which was strikingly similar to that described in Case 3. Remissions in these signs were noted. The Argyll-Robertson pupils were misleading to many observers before periarteritis nodosa was discovered at operation. The Bell's palsy and facial paresthesiae were manifestations of cranial nerve involvement.

Case 6. History (Adm. 367887). A 21 year old Italian man was admitted to the service of Dr. G. Baehr on June 25, 1934 because of sharp, knife-like pain in the right flank of twenty-four hours' duration. Six months before admission he had pain and swelling of the ankles, anorexia, nausea and malaise. For six weeks prior to admission he had complained of pain in the knees, elbows and left wrist; he also had polyuria and polydipsia.

Examination. The patient was a thin, pallid youth complaining of pain in the right loin. The fundi revealed blurred discs and several recent hemorrhages and exudates. There was a soft systolic murmur at the apex. The second aortic sound

was markedly accentuated. The blood pressure was 190 systolic and 130 diastolic. The brachial and radial arteries were sclerosed. There was moderate tenderness and rigidity in the right upper quadrant and upper half of the right loin.

Laboratory data. Hemoglobin, 52 per cent; red blood cells, 3,200,000; white blood cells, 38,500; polymorphonuclear leucocytes, 93 per cent; lymphocytes, 5 per cent; monocytes, 2 per cent. The urine showed albumin, rare red blood cells and granular casts. An x-ray examination of the abdomen showed obliteration of the right psoas margin.

Course. An intravenous pyelogram showed marked compression of the right renal pelvis and an emergency operation was performed. A large perinephritic hematoma was discovered and emptied. The patient died suddenly several hours later.

Necropsy findings. A generalized periarteritis nodosa was found. On sectioning of the brain, there were no naked eye alterations. Microscopically the vessels in the brain showed thickening and inflammatory changes in the adventitia suggestive of periarteritis nodosa.

Comment. This case is described chiefly because periarteritic lesions were found in the brain. The polydipsia and polyuria may have been due to arteritic lesions in the region of the tuber cinerium at one time.

Case 7. History (Adm. 450970). An eight year old girl was admitted to the Pediatric Service on August 8, 1938 because of coryza and sinus disease of seven months' duration. In January 1938 the child had "bronchitis" which lasted three weeks. One week later she was given an injection of serum for a cold and following this she had a severe attack of asthma. Autogenous vaccine made from her antrum also produced a severe asthmatic reaction. For one week before admission she had daily fever of 101 to 103°F.

Examination. The patient was a chronically ill child who was orthopneic. The blood pressure was 110 systolic and 84 diastolic. There was tachycardia. There were no other signs of disease of the thoracic or abdominal viscerae.

Laboratory data. Hemoglobin, 92 per cent; red blood cells, 4,100,000; white blood cells, 17,200; eosinophiles, 49 per cent; polymorphonuclear leucocytes, 30 per cent; basophiles, 2 per cent; monocytes, 4 per cent; lymphocytes, 15 per cent.

Course. The child's hospital stay was prolonged and dramatic. She showed evidence of cardiac disease. The diastolic blood pressure was elevated. There were numerous and scattered petechiae and ecchymoses over the body. The temperature was elevated to 102.4°F., and anemia set in, the hemoglobin dropping to 60 per cent. The urine showed casts and red blood cells. Exudates and hemorrhages appeared in the right fundus. On September 15, 1941 she complained of headache in the left parietal region and pain in the left loin. One hour later she became semi-stuporous and twitching in the left face and upper extremity appeared, which soon spread to become a generalized convulsion. The blood pressure increased to new high levels of 200 systolic and 120 diastolic and 290 systolic and 130 diastolic. Lumbar puncture showed clear and colorless cerebrospinal fluid under a pressure of 180 mm. of water, with no cells and a total protein of 25 mg. per cent. Periarteritis nodosa was suspected. A biopsy of muscle and skin revealed nothing of significance. A neurological status revealed no gross abnormalities. The child continued to be listless. Diffuse vascular disease, periarteritis nodosa, chronic glomerulonephritis and allergy were considered. She was discharged and readmitted on three occasions for "sinusitis," asthma, renal and cardiac disease. A string of discrete nodules were felt along the course of the epigastric vessels. A biopsy of one of the nodules showed a segment of a thrombosed blood vessel with scattered collagen necrosis, few giant cells and eosinophilia. On January 12, 1940 she had a generalized convulsion, from which she never regained consciousness, and died.

Necropsy findings. Generalized periarteritis nodosa was found.

Comment. The convulsive seizures may have been due to hypertensive encephalopathy associated with renal damage. The retinal lesions described here and in Case 6 were probably the result of hypertension and kidney involvement. True periarteritic lesions of the retinal vessels are uncommon.

DISCUSSION

A review of our cases and those reported by others shows that one of the most characteristic and frequent nerve disorders in this disease is involvement of single nerves in the extremities. The involvement may be multiple but it is usually asymmetrical and the nerves are affected individually at different times. Regression in signs is also characteristic of the illness. Asymmetrical, multiple and single nerve palsies are otherwise rare, but do occur in periarteritis nodosa. As is well known, most of the neuritides are symmetrical. Isolated nerve palsies are found in injuries, local infections, compression, ischemics of nerves, and in leprosy. The neurological clinical picture in periarteritis nodosa may be classified as that of "mononeuritis multiplex." The term neuritis, however, is not strictly speaking correct, since there is no inflammation of the nerve tissue proper and there is true neuropathy.

The pathology has been described by many authors, e.g., Lorenz, Meyer, Schmincke and Kernohan and Woltman. Most of the peripheral nerve lesions are infarctions as the result of occlusion of the smaller nutrient vessels to the nerve trunks or bundles. Kernohan and Woltman found many infarcts, especially in the distal portions of the nerves, but they saw no signs of inflammation. Edema and widespread degeneration were noted even central to the site of vascular occlusion. These are not the only types of lesions of the peripheral nerve. Harkavy reported eosinophilic perineural infiltration of small nerve bundles found in a biopsy taken from the skin.

Lesions of the peripheral nerves seem to be more common than those in the central nervous system. There are no striking symptoms of gross lesions of the brain, such as hemiplegias, etc. because large vessels are rarely occluded. When, however, the brain or cord is examined histologically arteritis and periarteritis nodosa of the smaller and even larger vessels are found. When the vessels become thrombosed distal infarction occurs and the signs and symptoms which appear reflect the function of the region which happened to be involved. Multiple arteritis of the cerebral and meningeal vessels may give rise to the syndrome of meningo-encephalitis. This is not an infrequent finding and sometimes may simulate syphilis, as in our case with the Argyll-Robertson pupils. Chvostek and Weichselbaum reported similar findings. A majority of the lesions in the central nervous system in periarteritis are the result of arteritis of the cerebral or cord vessels, but when there is renal involvement with secondary hypertension and arteriosclerosis the resulting picture may be that of hypertensive encephalopathy. Many of the convulsive seizures may be

explained on this basis. When the meningeal vessels are involved subarachnoid hemorrhage may develop, as it did in one of our cases.

Cranial nerve involvement in periarteritis nodosa is not common but when it does exist it may assume any form. The facial nerve is the one most often affected. One of our cases showed diplopia due to abducens weakness. Retinal and optic nerve changes are common but they are difficult to interpret clinically because of the frequent occurrence of kidney disease and hypertension. Goldstein and Wexler have described periarteritic lesions in the arterioles of the choroid; such lesions of the retinal arteries are rare. Histologically the retinal lesions in cases of periarteritis nodosa are usually those found in association with hypertension and malignant sclerosis.

SUMMARY

Seven cases of periarteritis nodosa with neurological manifestations are described. The most characteristic nerve disorder in this disease is involvement of single or multiple peripheral nerves in the extremities. The nerves are usually affected individually and at different times. Signs of central nervous system involvement are also present but are never striking, chiefly because gross lesions of the brain or spinal cord in periarteritis nodosa are uncommon. Renal damage and associated arterial hypertension may explain some of the symptoms of brain involvement in periarteritis nodosa.

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SELF-OBSERVATIONS AND PSYCHOLOGIC REACTIONS OF MEDICAL STUDENT A. S. R. TO THE ONSET AND SYMPTOMS OF SUBACUTE BACTERIAL ENDOCARDITIS

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To understand and relieve the symptoms is still the main labor of the physician in the management of patients during the long and usually hopeless course of subacute bacterial endocarditis. Much has been written on the bacteriologic and immunologic aspects and on the post mortem findings in subacute bacterial endocarditis. The symptoms and subjective behavior of the patient, on the other hand, have received surprisingly little consideration, although the complaints are many and often puzzling. It is indeed a rare opportunity in any disease to obtain an intelligent and complete story in which subjective sensations are well related to objective findings.

A. S. R. was a fourth year student in the Harvard Medical School and a young man of exceptional ability. It is hoped that physicians may read with profit this record of his keen self-observations with its philosophical remarks, written during the course of a disease which he recognized as hopeless. With the exception of the headings and minor editorial changes and omissions, his observations are reported here as they were dictated by the patient.

CASE REPORT

History (Adm. 29669). A. S. R. was admitted to the Peter Bent Brigham Hospital on June 17, 1921, at the age of 13 with the complaint of "marked choreiform movements." The family and past histories were non-contributory.

Following several attacks of severe tonsillitis the patient's tonsils and adenoids were removed in 1920. Two months previous to his admission to the hospital he developed dyspnea on moderate exertion and one month before admission rheumatic fever. Almost simultaneously he developed chorea.

Examination. The significant findings were as follows. There were choreiform movements of the muscles of the face and extremities. The size of the heart was normal on percussion. A blowing systolic murmur was present over the apex. There was moderate swelling of the second joint of the fourth finger of the right hand. The arterial pressure was 120 systolic and 38 diastolic and subsequently 120 systolic and 0 diastolic. On July 19 a distant diastolic murmur was heard over the apex and a blowing aortic diastolic murmur over the base. The patient was free of choreiform movements by this time. On repeated examination the degree of enlargement of the heart was either slight or not appreciable. However, on August

3 the roentgenogram indicated a moderate degree of enlargement. The total transverse diameter was 13.2 cm. with a thoracic diameter of 24 cm. The temperature and heart rate were elevated during the first week, but subsequently returned to normal. The laboratory tests, with the exception of slight initial leucocytosis, were non-contributory. The serological test of the blood for syphilis was negative. The patient was discharged on August 16, 1921.

Course. The patient was followed in the Out-Door Department and one year later the only complaint was palpitation. The physical signs remained unchanged. The arterial pressure was 150 systolic and 0 diastolic. In June 1923 he suffered from a severe attack of pharyngitis and following this some of the joints became swollen. In 1926 he developed nose bleeds and headaches. Otherwise the physical signs showed no change, and the diagnosis was aortic insufficiency. He never exerted himself and did not experience dyspnea.

Second admission (Adm. 74933). The patient was readmitted to the Peter Bent Brigham Hospital on July 23, 1931. In the spring of 1931 following measurement of his blood pressure, he noted a small circle of subcutaneous red spots which did not fade on pressure. The patient suspected subacute bacterial endocarditis. A short time afterward, when he had run across a street, he developed showers of premature beats which lasted for ten days. The subsequent part of this illness will be described by the patient.

On examination in July 1931 he appeared somewhat anxious. The head was normal. There was marked visible pulsation of the carotid arteries with a thrill and a loud systolic murmur. The apex impulse was 13 cm. from the midline in the sixth space. There was a loud systolic and a high pitched diastolic murmur over the aortic area. The pulses were Corrigan in type. Pistol shots were heard over the brachial and femoral arteries, but Duroziez's sign was absent. The arterial pressure was 140 systolic and 0 diastolic. There was a small reddened streak on the dorsum of the right thumb. No petechiae were seen. The rest of the examination revealed no abnormal finding. Rheumatic fever with heart disease and with aortic insufficiency was diagnosed. The possibility of subacute bacterial endocarditis was considered. On August 2 a positive blood culture for streptococcus viridans was obtained, and thus the diagnosis of subacute bacterial endocarditis became established. On August 5 streptococcus hemolyticus, streptococcus viridans, and an indifferent strain of streptococcus antigens were injected intracutaneously on the flexor surface of the right forearm. The result was entirely negative. Various methods of treatment were tried without benefit. On August 24 he developed left upper quadrant pain. The electrocardiogram revealed premature beats. There was a moderate degree of leucocytosis present. The rest of the laboratory tests were non-contributory.

On September 11 the patient was transferred to the Boston City Hospital where the findings were as described above. His temperature varied from 100 to 101°F. The spleen was palpable. On September 14, 1931, tenderness and slight swelling of the right index finger developed with a vaguely circumscribed red spot. Arterial blood pressure was 130 to 170 systolic and 0 diastolic. The white cell count of the blood was 12,000 to 16,000 per cm. By September 18, 1931 numerous petechiae had appeared. The spleen became larger. Blood cultures were positive for streptococcus viridans. Urine and blood chemistry were normal. There was a slight degree of secondary anemia. On September 25 he developed an attack of acute pain under the left costal margin which became worse on inspiration. Extreme tenderness was experienced over the spleen. During the next two weeks various embolic manifestations, sore muscles and joints, and tender cutaneous nodules developed. Beginning with October 18 the patient developed transient attacks of aphasia and on October 21 complete right hemiplegia occurred. On October 26 he developed pulmonary edema and died.

Diagnosis. Rheumatic heart disease with subacute bacterial endocarditis. Aortic insufficiency. Embolic manifestations. Mycotic aneurysm of the cerebral vessels.

Necropsy. The pertinent findings were as follows. The heart weighed 620 Gm. The left ventricular wall was considerably hypertrophied. Both ventricles were dilated. The leaflets of the aortic valve were thickened and retracted, and slight fusion existed at the juncture of the cusps. There were numerous soft vegetations attached to the aortic cusps. The large ones projected into the lumen of the opening of the valves, growing mainly over the cardiac surface of the cusps. The vegetations continued downward toward or onto the aortic leaflet of the mitral valve. The mitral valve and the chordae tendineae failed to show any thickening or deformity. The tricuspid and pulmonary valves were normal. The coronary arteries were normal. The spleen was enlarged and somewhat soft. The upper pole was adhesive to the diaphragmatic surface with fresh fibrin. The surface showed three white areas, two large and one small, which on section corresponded to infarction. The right kidney was imbedded in a soft hemorrhagic mass. The coagulated blood ruptured the capsule, and the hemorrhage spread over the entire right retroperitoneal area from the diaphragm down to the cecum. The right kidney itself was pale and flattened. There was a small infarct present. The left kidney surface contained small petechial hemorrhages, but was otherwise normal.

There was a subarachnoid hemorrhage over the left fronto-parietal region. Necrosis was present in the internal capsule and lenticular nucleus on the left. Hemorrhage was present throughout the course of the left middle cerebral artery. Some of the larger vessels were plugged by a grayish fibrinous material, which seemed older than the degenerative lesion of the basal ganglia. The rest of the findings were not significant.

The *anatomic diagnoses* were: subacute bacterial endocarditis (aortic and mitral); old rheumatic endocarditis with aortic insufficiency; infarctions of the spleen, kidney and brain; left occipital cerebral hemorrhage; left fronto-parietal meningeal hemorrhage. Microscopic examination confirmed the gross anatomic diagnoses and in addition revealed an intracapillary glomerulonephritis. Culture of the blood obtained from one of the cardiac chambers yielded streptococcus viridans.

SELF-OBSERVATIONS

FEARS AND HANDICAPS BEFORE THE ONSET OF SUBACUTE BACTERIAL ENDOCARDITIS

"These notes constitute subjective experiences and observations during the course of a generally fatal disease. It is hoped that here and there, there may be a statement, which may prove of value in the elucidation of some medical problem or of some problem involving the psychology of the sick room.

"A Viennese psychologist is reputed to have said that the education of the child should begin twenty years before the child is born. In like manner, the pathogenesis of a disease must be sought usually in the records or reactions long antedating the immediate symptomatology. In this regard, I must look for the genesis of the present disease at least ten years back to the time when I was afflicted with chorea and rheumatic fever with resulting damage supposedly only to the aortic valve. The fact that the only or principal lesion was aortic is, of course, of significance in the understanding of later events. Aortic regurgitation, as is well known, carries with it a syndrome of hemodynamic phenomena, which are among the most striking in the entire field of physical diagnosis.

"For ten years now, I have carried a blood pressure ranging on the average of 160 systolic and 0 diastolic, a fact, which translated into physical emotions means, especially when we consider the existence of the *cor bovinum* of aortic insufficiency, that every ventricular systole is sensed by the patient with no effort on his part,

so that I might almost facetiously say that, if I did not sense the heart beating at any time, during the past ten years, I knew I was dead. The physical discomfort of being forced to experience every ventricular systole over a long period of years is not to be underestimated, and I had often felt willing to sacrifice many things in order to feel again how it was to be able to live without feeling my heart beat. With this physical and psychological handicap, I was able to complete perhaps with a little more than the average degree of success, school, college, and three-fourths of medical school.

"It was when I had acquired enough medical information to understand the clinical problems surrounding my particular case, that there began to shape themselves in my mind, three fears, as it were, relative to my ultimate fate, which albeit, I had not usually looked upon as being very near. I knew there were always three octopi ready to grab me in their tentacles at the first possible opportunity. The first of these was a recurrence of the rheumatic fever, the second was cardiac decompensation, for I was leading a very active life, and the third was subacute bacterial endocarditis."

SELF DIAGNOSIS AND THE EARLY COURSE OF THE DISEASE

"The possibility of my having subacute bacterial endocarditis first entered my mind about January 1931. I had no definite indication that I was affected with the disease except a strong neurotic inclination in that regard, and a subjective feeling of fullness in the right upper quadrant, which I thought might be an enlarged liver. I had never felt my liver edge, although in the hot bath I had felt something in the right upper quadrant concerning the nature of which I could not satisfy myself. I have no reason to believe at this time that a large liver was a sign of subacute bacterial endocarditis, but what with the mental attitude that I had plus another idea that my fingers were somewhat clubbed—again an idea for which I had no definite proof—I thought the wisest policy would be to consult those who knew more about medicine than I did, and I repaired to the office of Dr. A., who reassured me to the extent that he could find no signs of subacute bacterial endocarditis existent at that time. He told me in that examination the signs of fullness and possibly tenderness in the right upper quadrant might well be due to gall bladder pathology independent of any other condition I had, inasmuch as the former was so common.

"I thought nothing more of my health till the following April, I believe, when I was taken to bed with an attack of acute tonsillitis. This occurred during a time when I was taking laryngology, and I thought I might have contracted tonsillitis from one of my patients. The attack was severe enough to keep me in bed for two or three days, but was readily relieved by the continuous sipping of cracked ice and occasional throat gargles. At the time subacute bacterial endocarditis did not enter my mind at all, the only consternation arising at all being the fear of the possibility of the subsequent acute or subacute nephritis. This fear was dissipated in due time by almost daily examinations of the urine which showed no blood cells or other abnormal findings.

"Things went along smoothly until, as I recall it, about toward the end of May. I was studying intensively for final examinations at the time, when I vividly recall running across the street to my house to avoid an oncoming automobile, an act which was followed by a procession of extrasystoles unprecedented in their frequency. At the time I thought that this condition would quiet down, but instead it seemed to grow worse. Study became almost impossible, sleep became well-nigh impossible. In fact, life itself was almost intolerable due to the almost never absent extrasystoles. If I had not known exactly what they were, I should readily have diagnosed the condition as auricular fibrillation. The condition was doubly intolerable due to the fact that I was trying to study medicine at the time, and each known fact seemed

literally to be hammered into my head by a cannon. I was able to devise no method by which I could obtain relief from these terrible extrasystoles, with the possible exception that at night getting up and walking around, thus increasing the heart rate, might lend some relief. Finally I decided to go to my family physician, not that I thought he could do very much for me, but simply to share my burden with him. He confirmed my diagnosis of extrasystoles, and advised me to see Dr. A. for further suggestions. During the course of the examination, he took my blood pressure, which showed no remarkable change, and he endeavored to reassure me from a psychological point of view.

"I cannot remember whether this took place before or after the final examination in medicine, which if I remember correctly, was scheduled on May 29. It may be that I had already taken that examination, and was studying for the National Boards, two of which I had yet to take. At any rate, at approximately one-quarter to twelve that night, I remember distinctly getting up from my chair and from the table, where my books lay, and taking off my suit coat. No sooner had I removed the left arm of my coat, than there was on the ventral aspect of my left wrist a sight which I never shall forget until I die. There greeted my eyes about fifteen or twenty bright red, slightly raised, hemorrhagic spots about 1 millimeter in diameter which did not fade on pressure and which stood defiant, as if they were challenging the very gods of Olympus. I had never seen such a sight before, I have never seen such a sight since, and I hope I shall never see such a sight again. I took one glance at the pretty little collection of spots and turned to my sister-in-law, who was standing nearby, and calmly said: "I shall be dead within six months." There was no mistaking what the sign was. It had only to be read. I knew that the pressure of the sphygmomanometer cuff might produce petechiae in the underlying skin, but I had seen petechiae before, and no stretch of the imagination could convince me that what confronted my eyes on that fateful night was due to any blood pressure cuff. Moreover, pressure petechiae more often occur under the cuff than so far distal to it, although the latter condition may very well occur.

"My sister-in-law naturally thought I was a little demented to make such a startling statement out of a clear sky at such an hour of the night, particularly as she knew absolutely nothing about my past medical history. It was impossible for me under the conditions to go to bed, as she advised.

"It was now just about past midnight, and in my quandry my eye caught the telephone. I had to talk with some one of responsibility. I called up Dr. A. whom I knew personally, knowing very little what I should say to him or do after he answered my call. Any doubts as to what I should say to him at this hour of the morning, were soon laid aside by my receiving the information that the doctor was out of town, I think attending a convention. I then called Dr. B. who lived much nearer to me than Dr. A., and whom it would be much easier for me to see at that time, should he agree to see me; but as fate would have it, he was also away, I think at the same convention, if it was a convention, as Dr. A. There was nothing left to do at this juncture, but to gather my nervous forces together at full composure, which I did. I collected myself, as it were, and then went to bed for the night. It was hard falling asleep that night. Every time I found myself awake, I would make a very conscious effort to return to sleep, a very annoying process indeed. By morning, the red spots were still present, although not nearly so red as they were the night before. Their significance continued to weigh on my mind, although for some reason, not nearly so heavily as on the preceding night, perhaps because the critical stage, as it were, was over. By the following morning the spots had practically faded away entirely, and with their disappearance went the only really tangible demonstration that I had subacute bacterial endocarditis. What I mean to say is that these petechiae have been the only external visible sign I had during the en-

tire course of the disease to prove the nature of my affliction. The fact that they did not reappear in any form or in any place, proved a little embarrassing to me in the following weeks, when I tried to convince associates and house officers that I had malignant endocarditis. It was difficult for them to make any diagnosis on what only I, perhaps a neurotic patient, and no one else had seen.

"I cannot remember in any detail the exact course of events in the days and weeks following my observation of the petechiae. This fact must impress the medical reader of the difficulty of eliciting accurate histories from even the most intelligent of patients. When I consider that so important a series of events in my life, and a series which happened less than four months ago cannot be recounted with any accuracy even allowing for any mental retrogression which might have taken place within me, I realize how futile is much of the detailed history taking resorted to on the wards, but that is but a digression. I shall have to gather the thread of the narrative at a date somewhere around the beginning of July. I had noticed here and there small short red streaks on my fingers perhaps only four or five or less on various days. These were apparently insignificant light red lines, ranging from one-eighth to one-quarter of an inch in length. I say they were apparently insignificant, and under normal conditions, I would consider them as such, but in my existing state where I was examining my hands every day for petechiae and embolic phenomena, I could not help being impressed with the occasional sudden appearance of one of these lines on my forefinger. I wish to emphasize that they were hardly noticeable, and if I were not looking for untoward phenomena, I should certainly not have given them any recognition. As it was, however, they were sufficient to set me on edge.

"I think it was on a Friday night that I was no longer able to tolerate these nagging omens. At about 7:00 o'clock that night I called up Dr. C. and asked him whether I could see him at once. It so happened that he had a concert engagement that evening which was scheduled to begin very shortly after I called him, so that the best I could do was to make an appointment for the following morning at the X Hospital. That Friday night was another night spent in considerable anguish. I got to feeling that I did not care whether or not I had subacute bacterial endocarditis, but I only wanted to know whether I had it and get the suspense over with. The following morning I saw Dr. C. at 9:00 o'clock, and he made a careful examination of me, including blood cultures and skin tests. On Monday morning, I saw Dr. C. again, and the skin tests were ready to be read. They were all highly positive, except that in which the streptococcus viridans was used as an antigen which was neutral, a sort of circular discoloration, which still persists. These readings were regarded as favorable since, as I understand it, in cases in which the body is immune to the organism of subacute bacterial endocarditis, these rheumatic skin tests are positive, whatever the immunological basis may be.

"Following this conference with Dr. C., matters progressed in a fairly normal manner for about a week or so. As I recall it, however, an occasional red streak appeared here and there among my fingers. I could find them in no other part of my body. Dr. C. had expressed his opinion that the phenomena which I was experiencing were simply part of a mild attack of rheumatic fever, assuming a somewhat abnormal form.

"Incidentally during a trip to New York, which lasted almost two weeks, I gained several pounds in weight despite the fact that I was very active during the entire time, and secondly I met a young lady with whom I became quite familiar and whose sister had died three or four weeks previously of subacute bacterial endocarditis, a fact which I did not learn for some days after meeting the girl, and a fact which did very little to calm my uneasy mind. During the same time I learned of the death of a school classmate of mine from subacute bacterial endocarditis, and I spent

some time listening to the details of the horrors of the mode of exodus. This particular young man, some two weeks before his death, was seized with an attack of aphonia while talking to a friend of his; later, I believe, with paralysis of the limbs; finally with coma, and death.

"On Wednesday with the kindness of the surgical resident of the Y Hospital and with the courtesy of his staff, I began my Fourth Year course and enjoyed it. Things went along fine. I weighed myself daily, never lost any weight, and occasionally gained some. On the Friday of the second week in which I started surgery, I began to notice some soreness in the back of my right knee at about noontime. That morning I had stood in the operating room for some three or four hours and attributed the soreness to that fact. I was sure it was simply some lameness of the ligaments behind the knee joint, although in orthopedic problems, I could never be anatomically definite.

"I did not think the matter serious enough to prevent me from walking up the hill from S. Street to R. Square to have lunch, although I might just as well have eaten directly across the street from the hospital. As the afternoon progressed, I began to notice the soreness more and about four or five o'clock noticed that I was limping, my right leg being the seat of the trouble. I did not leave the hospital till about seven o'clock that night, and I would have stayed even longer, had I felt well, for there were still one or two histories which I should have taken. I was barely able to reach home that Friday night, for it was some walking distance from the street car to the place where I was living. I had to stop several times along the way for a little rest and then was able to drag my foot along. I had dinner that night with the family, and then lay down, thinking that the soreness would soon pass over. However, it increased rather than decreased in magnitude, and at about nine o'clock, I was forced to call my family physician. All this time absolutely nothing else entered my mind except the diagnosis of some affection of the ligaments of the knee joint. My physician, however, made a diagnosis of rheumatic fever, even though there was nothing to observe in the joint which was not red, or swollen, or edematous, or hot; in fact, he made the observation that the right knee joint, if anything, seemed cooler to the touch than the left. I accepted his diagnosis with some reluctance and entered upon anti-rheumatic therapy, heavy doses of aspirin and oil of wintergreen packs to the knee joint. There was no fever at the time. The pain in the knee continued for several days despite the intense anti-rheumatic therapy, but the temperature was always normal at the time it was taken by my family physician. My own thermometer, however, showed slight elevations in the lower 99's when I took it in between his visits. By the Wednesday of the following week, I began to become a little worried over the condition which showed no tendency to clear up, as did my family physician. We decided at that time to call Dr. A. in consultation, and he appeared on the scene Wednesday night about 10:30. Dr. A. also made a diagnosis of rheumatic fever, and advised my immediate removal to the Hospital. I had expressed to Dr. A. at the house my fear of subacute bacterial endocarditis, but again I had no signs to show him. He told me at some time later that he did feel my spleen on that night, although of course, he did not impart the information to me at the time; however, as I said, his admission diagnosis was rheumatic fever."

IN THE HOSPITAL

Bacteriologic confirmation of subacute bacterial endocarditis; treatment

"As a new patient, I went through the ordinary routine of examination and investigation. The house officer took my history and asked for my chief complaint. I told him 'subacute bacterial endocarditis.' He laughed heartily as did the resident

when he came up later. Both told me that they thought very little of my chief complaint and both again made the diagnosis of rheumatic fever, a diagnosis which was becoming increasingly repugnant to me, because there was so little somatically to uphold such a diagnosis. I was put on an anti-rheumatic regime again, and was prescribed a diet of salicylates and bicarbonates to the extent of one gram of each per hour not until I should be affected with ringing in the ears, but until I should hear cathedral bells ringing in my ears. This was a fortunate modification, for tinnitus began after the first or second dose of salicylates, while the cathedral bells did not begin to sound until some 24 doses had been taken. Nausea had also set in at this time—quite naturally. I had by this time developed a temperature which ranged between 99 to 100°F. and which was not affected by the salicylates. The conclusion reached by the service was that the case was simply one which was resistant to salicylate therapy, not an uncommon occurrence even in rheumatic fever, and the drug was continued on smaller doses. The possibility of infectious arthritis was also raised at this time which was one to which I had less animosity at this time particularly since my tonsils were somewhat uncomfortable though giving me no real trouble. A blood culture taken previously was negative, as were other laboratory tests. While the diagnosis of infectious arthritis was under consideration, a second blood culture was taken, and my fate was sealed. The green producing streptococcus was found on the culture medium, and the diagnosis which I stoutly defended for more than a month, against the protests of all those around me, now was unfortunately confirmed.

"I had had a very embarrassing time trying to convince visiting men and house officers that I had subacute bacterial endocarditis, because all I could do was to describe signs which I only, and no other had seen. I even went so far one morning as to point out to Dr. A. on ward rounds certain cutaneous manifestations on the chest of another patient which I told him resembled the petechial hemorrhages which I had observed on myself the preceding May, but now everything was changed.

"I well remember the morning when Dr. D. and Dr. A. approached my bed with sober faces. I rather suspected that something was up when I saw them coming toward me, but I was not exactly sure what that something was. Finally Dr. A. imparted to me the information that the last blood culture was very suspicious. He all but said that it was positive for streptococcus viridans. Here was the last link in the chain. I had previously had inculcated into me the fact that I was going to die within a comparatively short period of time, but I could always find a leeway out. I could always find a loophole in the evidence here and there howsoever untenable I knew these loopholes to be, but now I was confronted with the *dictum ultimum* from which there was no escape. I do not exactly recall my reaction to this message from the Angel of Death, although as I remember it, I showed no emotional change whatsoever. I calmly accepted the news from my two physicians and immediately brought up before them a project which I had considered before in my mind and which I think I had already mentioned to Dr. A.—the idea of going to the Rockefeller Institute as a patient for experimental investigation—to submit myself to the Institute as an experimental animal to do with whatever they desired. My reason was that by this plan I had nothing to lose, possibly something to gain, and in any case, science would be the benefactor, whereas, under other conditions perhaps no one would derive any advantage from my illness. The idea of going to the Rockefeller Institute seemed to appeal to both Doctors A. and D. and one of them got in touch with the Institute by rapid communication to find out what the possibilities were. As fate would have it, it so happened that Dr. E. who would have been the chief attraction for me to go to New York, was away on his vacation. So also was Dr. F. and also Dr. G. The only one left, I gathered, at the Institute was a resident who was none too enthusiastic about accepting the responsibility of admitting a Fourth Year

Harvard Medical Student with a fatal disease. The upshot of the matter was that I remained in Boston.

"I was frequently visited in the hospital by a classmate of mine at the Medical School, whose 17 year old sister it appears had about a month before, been seized with an attack of streptococcus meningitis and septicemia. She was apparently dying at the Massachusetts Eye and Ear Infirmary, where I believe they had never seen a recovery from such a combination of conditions. Someone at the time suggested the use of Pregl's solution, an iodine containing preparation used intravenously, and to the surprise of all, the young lady recovered with this therapy. I understand also that a subsequent such case was similarly cured at the Infirmary. Naturally, the idea suggested itself to me that my own blood stream might be sterilized by a similar procedure. I advanced the proposition to Dr. D. who was willing to try it. He tried the Pregl's in doses, of the exact magnitude of which I am ignorant, but which I believe ranged around 30 cc., and these injections were repeated at daily intervals for some three or four days. The temperature curve seemed to show some reaction to the drug, and at one time there seemed to be a definite downward tendency of temperature, but as fate would have it, about the same time occurred the first of my splenic infarcts which set all observations topsy turvy. It so happened, however, that another patient, a boy about 17 years old in the ward, also suffering from subacute bacterial endocarditis, was accorded the same treatment, and he apparently suffered from no phenomena, which made the observation worthless, and although his temperature also showed some peculiar reaction to the drug, the final result was negative. As I look back on this therapeutic procedure, it seems only logical that it should be a failure, for even though the blood stream were sterilized for a day or more, as soon as the drug was out of the system, the original focus would become active again, and the disease take its natural course. The splenic infarct which interrupted the Pregl's treatment held things up for some time. Things gradually returned to their previous status, and the question arose again as to what to do. It was suggested by Dr. D. at this time that the use of sodium cacodylate be tried, for it appears that someone some years before, reported some six or eight cases cured by the use of this arsenical. Sodium cacodylate was administered intravenously for three or four days and no toxic symptoms supervened such as garlicy odor to the breath. By this time I was quite reconciled to my fate, but nevertheless was continuously seeking new treatment. I am entirely sincere when I say that I sought new treatments not in any serious endeavor to cure the disease or prolong my life, but simply to satisfy the urge that something be done. The psychological factor was now of most importance, and if I were to lie in bed much longer, I needed the moral satisfaction of having something done to me, however useless it might be.

"At this time I was informed by one of the post-graduate students of the apparently successful use of polyvalent anti-streptococcus serum in cases of subacute bacterial endocarditis. It seemed the next logical step to follow up, and again I secured the consent of Dr. D. to try this treatment. Skin tests for protein sensitivity were performed, and to my disgust were found to be highly positive, that is, I was quite sensitive to the serum. This meant that I should have to become desensitized, a procedure, the discomfort of which every practicing physician knows. At any rate I was willing to submit to the discomfort, despite the assurance of Dr. D. that the treatment would do me no good. Dr. D. did his best to discourage me, so it seemed, from submitting to the course of serum inoculations by painting to me the black picture of serum sickness with its arthralgia and pruritus, but nothing daunted me. That Sunday afternoon, for it was on Sunday, we began the serum treatments, first into the skin, then under the skin, then into the muscle, finally into the vein."

Splenic infarcts and observations on the effects of morphine

"One of the most dramatic episodes in clinical medicine is the splenic infarct which occurs in malignant endocarditis. In its histrionic appeal, it must be classed with coronary thrombosis, acute mesenteric occlusion and postoperative pulmonary embolism. However, at least from the basis of my own experience, I am forced to wonder whether the splenic infarct is exactly what the older clinicians, such as Osler and Janeway have described it to be. These gentlemen describe the splenic infarct as an event occurring with indescribable suddenness and accompanied by intolerable pain. If I remember correctly, Osler remarks that an embolus to the spleen may be the first warning and only sign of a deep-rooted ulcerative endocarditis. It is certain, no matter in what light we look at the acuteness of the infarct that the possibility of its existence should be always considered by surgeons in making a differential diagnosis of the so-called acute abdomen.

"It is my impression that I have suffered two infarcts of the spleen; the first occurred several weeks ago at another hospital, and it might be worthwhile to say a word about its onset. Its onset was certainly anything but vitally acute. At approximately midnight I noticed that it was slightly uncomfortable for me to lie on my left side, although I was unable to localize any definite discomfort. One or two hours later it became uncomfortable for me to lie on my back, and by about 3 o'clock I was generally uncomfortable. At 4 o'clock I was sitting up in bed, and it became apparent to the night nurse, although I volunteered no information to her that I was in distress. She questioned me concerning the nature of my discomfort, and I explained it to her as succinctly as I could. She asked me whether I wanted her to call the House Officer, but I asked her not to for several reasons. The main reason was that I did not want to disturb him at that hour of the night, although I felt utterly certain that he was regularly awakened for much less justifiable causes, nor did I wish to give any one the impression that I was taking undue advantage of my status as a medical student in seeking assistance—a factor which often moved me in a similar manner. At 5 o'clock the pain in the left upper quadrant became intolerable.

"The diagnosis of a splenic infarct in this case was not absolutely confirmed, but there can be no doubt of its correctness even though no friction rub was heard by the visiting man. Diaphragmatic pleurisy was ruled out on general principles, the only other important possibility remaining being a renal infarct which, of course, I feared inestimably more than a splenic infarct. I could have not many qualms about losing a few cubic centimeters of an organ, which physiologists have never found too much use for, but the prospect of renal infarct brought up within me visions of that famous party of uremia, convulsions, coma, and death. It was with a certain amount of fear that I observed the color of my urine in those days following that infarct, for after all hematuria would have clinched the diagnosis. The fact that I was taking a variety of drugs at the time, mainly soporifics and was probably affected with hematoporphyrinuria, made the diagnosis of gross hematuria not an easy one. The pain of this embolic phenomenon disappeared by the following night, and conditions returned essentially to what they were previously.

"The second occasion, in which I am forced to the conclusion that my spleen has been infarcted, took place yesterday. Here again the onset of the whole affair was remarkably similar to the first one. There was no suddenness or acuteness about the onset. The realization was only gradually forced upon me that I had again pain in the left upper quadrant, and as before, the pain reached its maximum intensity gradually and not suddenly. However, in this second case the pain was very much more severe than in the first, and it was very comforting to me in my agony that I had such medical and nursing service at my immediate call as I should require.

It was absolutely impossible for me to lie down in any position, on the left side, on the right side, or on the back. One attempt to lie on the right side caused such a piercing, lancing pain in the region of the spleen that I was left with a fear of even turning on my right side for hours afterwards. It was a pain indescribable in its intensity. It was impossible for me to take an inspiration of any appreciable length. As a result, my respiration increased remarkably both in frequency and shallowness and with it my pulse rate. The fact that the pain has been lasting more than the usual amount of time considered proper for an infarction has made me think at times that the seat of the difficulty might have been a very rapid enlargement of the spleen. The physical examination, as well as other considerations, have ruled this possibility out.

"More than a year ago I delivered obstetrically twelve women, and I think I can truthfully say that the suffering I endured in the last two days or so is certainly no less than that borne by perhaps half my patients on district.

"Since this note was written the pains in the left upper quadrant have returned to almost their previous intensity—(Saturday morning). This time instead of straight morphine we tried Schlesinger's solution hypodermically which I believe contained one-sixth of morphine and one-two hundredth of scopolamine. The amount of morphine in this combination was obviously too small to affect the pain: in fact, I was still not able to lie back in any direction but through the use of two pillows set upon a cardiac table which in turn was set before me, I was able to snatch a few minutes of sleep here and there over a period, however, not exceeding a half hour. In short, it seemed to me that the combination of scopolamine and morphine in the proportions stated, was in no way as effective as the straight one-quarter of morphine to which I had been accustomed.

"It seems to me also that the pain in the region of the spleen is intensified not only by lying in any direction, but by drinking fluids, and I wonder whether this might not be due to the fact that even the slightest distention of the stomach causing pressure on the already sensitive spleen, might cause an additional amount of pain, however small, the spleen being one of the anatomical relations of the stomach. So far as I know, no physical sign, such as a friction rub has yet been elicited which definitely proved the existence of the splenic infarct although increased leucocytosis, I believe, has put in its appearance, which finding takes place in the occurrence of any organic infarction including that of the heart.

"I felt sure that I was going to collapse momentarily from sheer exhaustion induced by lack of sleep and the intense pain. I cannot deny that I had visions of the end, nevertheless, I knew that morphine would soon take the edge off the pain, at least, if I could only get it quickly enough. Thanks to the foresight of my physicians, and I might humbly add, perhaps also to their confidence that I would not abuse the privilege, their standing orders permitting me to call for reasonable doses of morphine within proper limits of time as I should find it necessary, proved a great boon in these days. I utilized this privilege comparatively little in the past, but was only too ready to ask for one-quarter of morphine at this time to relieve the intense distress which was gripping me. This dose seemed to take the edge off the pain sufficiently to allow me to lie on my right side for perhaps ten or fifteen minutes during which time I fell readily into a sleep following the exhausting experiences of the past hours. The effect of the drug, however, soon wore off, and I was forced to seek its assistance again, and perhaps sooner than was customary, and I continued, as I recall it, to take the drug most of the time orally for the next day.

"It has been my own personal experience with morphine that it is just as effective taken orally as parenterally. On the other hand, I feel that I have a certain paradoxical reaction to the drug. There have been no pleasant subjective reactions accompanying its use such as one might suppose might be present from the stories

one hears or reads of morphine addiction. Certainly in the 20 or 30 times or more that I have had hypodermic administrations of the drug, I have experienced no sensation or other reaction which would urge me to seek its fruits again. In fact often nausea would be the outstanding contribution of the drug to my system, not to mention again those cases we spoke of before when the pain of the injection was the major contribution thereof. I might repeat for emphasis that whatever pleasures may be inherent in cocaine sniffing or in opium smoking, the God of Morpheus has offered very little to tempt me. In fact, I recall vividly now a time when I was suffering from my first splenic infarct and was taking morphine rather frequently when I expressed a fear to Dr. H., who very kindly happened to visit me at this time, that I might become an addict. He very intelligently told me then, that the present problem was to remain as comfortable as possible and that after recovery, we could look to the problem of the morals of morphine addiction, should the problem exist.

"Splenectomy has been recommended in the literature in the treatment of malignant endocarditis, but it has not found much favor. I do not know the exact rationale behind this procedure, but it must have a decided advantage in relieving the patient of the abominable misery accompanying splenic infarction. On the other hand, the regularity and frequency with which splenic infarction takes place in this disease causes us to consider the spleen a *locus minoris resistentiae*; and we can at least conceive that other more important organs of the body would undoubtedly be the recipients of the emboli which would have gone to the spleen, had it been present.

"In conclusion I do not wish to leave the simple impression that splenic infarction does not occur with great suddenness. I simply think that it is nearer the truth to say that maximum intensity of the pain is reached in a comparatively short time as opposed to its instantaneous occurrence. Undoubtedly there might be much more said about the rôle of the spleen in subacute bacterial endocarditis, but I think I shall have to leave the subject of the spleen here and in a subsequent note go on to another topic.

"Indeed, one is reminded of the story of the German Professor of Physiology who said: 'Gentlemen: we come now to the story of the spleen. We know nothing of the spleen. So much for the spleen. We will now take up the liver.'"

Extrasystoles

"It is not so many years now since Sir James MacKenzie pointed out to the medical profession the more common types of cardiac arrhythmias and especially the prognostic imports. One of the most common of these irregularities of the heart beat is, of course, the extrasystole which is more popularly known as a skipped beat. It was MacKenzie who first pointed out generally the harmless nature of this phenomenon, and the later textbooks have taken up the letter which MacKenzie so forcefully laid down. The textbooks and the later writers all have accepted in a general way MacKenzie's dictum as to the favorableness of the prognosis accompanying extrasystoles, and they all mention the fact that the chief harm inherent in the extrasystole lies in the discomfort sometimes caused the patient.

"My own experience with extrasystoles has been a rather long and varied one. Extrasystoles in myself have been particularly distressing phenomena, much more so than one would glean from the textbooks and from the manner in which clinicians put aside the average patient's complaint as to skip beats. The sensation experienced by me in the presence of an extrasystole is almost indescribable. It will be remembered from the physiology of the extrasystole that the second or so-called compensatory beat sends forth not only the amount of blood which would be emitted in an ordinary ventricular systole, but the amount which the ventricle has received during the so-called compensatory pause. Now, when we consider the fact that in

aortic regurgitation the left ventricle is already hypertrophied and dilated in its, shall we say, normal state how much greater must be the output when we consider the fact that the filling time has been prolonged more than usual. This means that the impetus or the violence of the systolic stroke must be terrific, and certainly that fact is reflected in the patient's system. The extrasystole has always affected me as if it were a cannon ball, shot point blank at my brain. The sensation is that of a terrific explosion, occurring within the narrow and limited confines of a calcified skull, which refuses to yield to the compressive force. It is like an irresistible force against an immovable object. Most of the time I am helpless before it and simply wait patiently in terror until the ordeal has passed. I have never been able to satisfy myself as to why I never suffered the sequelae of a cerebral accident following an extrasystole, for I can think of no other sensation which can so closely simulate breaking of any blood vessel in the brain without doing so. I cannot say with any definitiveness that there are any special factors which induce the extrasystole.

"I remember one particular couch in a house in which I lived once; and it seemed that every time I lay down on that couch the natural consequence would be a flurry of extrasystoles. No sooner did I get up than the phenomena ceased. I have more recently been impressed with the frequency of extrasystoles following the administration of morphine, and I attributed the former to the latter, I don't know with how much justification, perhaps it was just a case *post hoc ergo propter hoc*. For my own satisfaction, I reasoned in the following way: that the extrasystoles were more productive of emboli than the ordinary ventricular systole, due to a much greater force of the ventricular beat against the aortic ring with its vegetations. This seemed to me to be a simple matter of physics which required no explanation or elaboration. I had moreover come under the impression that morphine caused an increased number of extrasystoles in my case due perhaps to the fact that it had a tendency to slow the pulse rate. While it is well known that in those persons susceptible to extrasystoles the latter occur with much more facility when the heart rate is slow than when it is fast, this phenomenon can be explained with more or less satisfaction by cardiac physiologists. So far as my own case was concerned, however, I had to deal with a circle, as it were. Morphine caused extrasystoles, extrasystoles caused emboli, more emboli required more morphine, and so the merry trio ran its course.

"One possibility of breaking up this ring presented itself to me, that was a possible ingestion of quinine sulphate 0.2 to 0.3 grams t.i.d. but there was one great drawback to even this solution. I had some months ago attempted to stop a series of extrasystoles through the use of quinine sulphate, and the night following the administration of the drug, I was seized with one or two attacks of paroxysmal tachycardia. The latter phenomenon phased me not at all, for I had experienced them before. Moreover, I was always entirely able to control these attacks by taking a long deep inspiration and holding it, under which conditions I could always feel the last of the paroxysmal beats. On the other hand, the other common methods of stopping the paroxysmal attack were never successful in my case. I had even at times attempted the very dangerous exploit of exerting double vagal pressure against all the advice of famous clinicians and authors, but this procedure neither killed me nor stopped my attack of paroxysmal tachycardia. The following consideration entered my mind in the present case. If I should take quinine to break up the series of extrasystoles, and if my previous experience should be repeated, and I should be again affected with an attack of paroxysmal tachycardia, how could I stop it? The natural answer would seem to be, by a deep inspiration, but it must not be forgotten that during this time I was undergoing the painful tortures of splenic infarction, and I had all I could do getting enough air into my system through a rapid series of shallow breaths. Any inspiration, let alone one which could be held

which would have the slightest effect on terminating the paroxysm, was as far from the realms of possibility, as one can imagine. The upshot of the whole matter was that it was left in *status quo ante bellum* so to speak.

"Since the splenic attack and since the diminution in the intake of morphine, the number of extrasystoles has decreased markedly: so has the number of embolic phenomena. I cannot prove that there is any relation existent among these three things, morphine, extrasystoles, and emboli, but the evidence, both therapeutic and clinical, is very strongly suggestive.

"There are certain settings in medicine in which the wise physician does not dare to take lightly the word of the patient or his family. When the mother of the child with intestinal intussusception tells the physician that the child has never before in all its aches and pains experienced anything like the present distress, the physician will not lightly cast such a statement aside. The patient who has had angina for years will not be slow to distinguish an attack of chronic thrombosis from anything he has ever suffered in the past, no matter how painful. In like manner, patients with common difficulties, will often discover their own little methods of relieving their symptoms without assistance of the physician. The patient with peptic ulcer, discovers the healing powers of sodium bicarbonate. The patient with angina discovers the beneficial effects of whiskey, little knowing that the latter contains nitroglycerine, etc.

"Not so long ago I had discovered that I could abort the worst effects of the extrasystole by exerting a forced expiration at the time when I felt the second beat was coming. The success of this little trick has been very encouraging at times and often I have felt that I have freed myself from God knows what, merely by breathing out the last drop of breath that was in me when I felt the extrasystole coming. Once or twice in the past, I have tried the opposite tactic of taking a deep breath and holding it when I expected the extrasystole. In these cases the force of the blow was tremendously exaggerated, usually striking in its full force within the cranium, less frequently in the carotid in the neck, but always in pistol-shot fashion. I have no doubt that the physiology of these various mechanisms can be very easily worked out in terms of filling of the left ventricle and related factors."

Clubbing of the fingers

"Clubbing of the fingers has long gone under the very pretentious name of hypertrophic pulmonary osteo-arthritis. It is said to be an outstanding sign in all thoracic infections and perhaps in a few others. The mechanism of the process is not clear. Although at various times within the past two or three years, I had suspected that my fingers had taken on a clubbed aspect, I could never be sure. It was one of those cases in medicine where one might say that if the sign was not definite, it was absent. The shape of the normal finger is so varied anyhow, that it does not take much persuasion one way or another to convince one that abnormalities of form are present. The remarkable point which I wish to bring out here is that I can almost say that I saw at least two of my fingers becoming clubbed under my own eyes. I can almost name the day when the process began, and this was about five weeks after the diagnosis was made. The first thing I observed was a gradual dropping away of the fleshy part of the nail, just as dying lilies have a certain reputation for drooping. In the meantime, the nail had become more nearly square in shape, although more round whether lateral or longitudinal was remarked. This process has taken place most notably in the middle fingers of both hands, and there have been only suggestions of the same in other fingers. Together with the squaring of the nail, it appears that there has been some change in the direction of the growth,

so that it appears perhaps that instead of growing absolutely straight out, it takes a somewhat devious course. There has been no particularly marked bulbous enlargement of the finger tip or other characteristics associated with clubbed fingers which have been so carefully reviewed in the German and American literature. There is no reason to believe that these changes are not in the process of development. The curious observation is that the two forefingers which most resemble clubbed fingers, have in truth undergone practically no change since the beginning of the disease, but have always, so far as I can remember, possessed the same shape. Possibly, there has been some deviation in the direction of growth in the nail."

COMMENT

The case of A. S. R. is a classical instance of subacute bacterial endocarditis in which an unusual combination of factors made it possible to obtain complete information on the disease. The observations reported give a correlated account of the subjective reactions as well as of the symptoms, signs, and structural characteristics of the disease.

A. S. R. was a somewhat high-strung, emotional and ambitious person. His original home environment was culturally simple and economically poor, and throughout his educational career he had to overcome handicaps. His economic and physical handicaps were incentives to achievement and success. To him, achievement essentially meant a denial of his handicaps. In considering his psychologic reactions it is of interest that before the diagnosis of his disease fears and conflicts were uppermost, but after the diagnosis was established, he took a certain amount of relief and compensatory satisfaction in objectivity toward his physical state. It is not unusual to find patients attempting to solve their anxiety by means of intellectualization. Even during this stage of apparent objectivity, however, emotionally A. S. R. was willing to try any method of treatment. "By this time I was quite reconciled to my fate, but nevertheless was continually seeking new treatment. I am entirely sincere when I say that I sought new treatments not in any serious endeavor to cure the disease or prolong my life, but simply to satisfy the urge that something be done. The psychological factor was now of most importance, and if I were to be in bed much longer, I needed the moral satisfaction of having something done to me, however useless it might be." This attitude is considered an expression of his underlying and apparently intellectually compensated anxiety. Translated into another concept, one may say that once his ego was threatened, emotionally he was willing to identify himself with any symbol of hope or courage. Later as his disease progressed, his suppressed fears returned to the surface with increasing frequency, and ultimately reactions of panic occurred. During this period of his disease loneliness was tolerated with increasing difficulty. Fears, impatience and mental depression could be best alleviated not by drugs but by the constant sympathy and encouragement of nurses and physicians, whose symbolic sig-

nificance increased with the fuller realization of the gravity of the medical situation. In other words the psychologic mechanisms operating to control his anxiety failed eventually. Regression to more infantile levels of demanding attention, sympathy and comfort became more and more apparent as his disease progressed. Thus the emotional reaction of A. S. R. to subacute bacterial endocarditis was not fundamentally different from that of any other person suffering from a hopeless disease.

Subacute bacterial endocarditis represents a particularly difficult task in psychotherapeutic management, because frequently, notwithstanding the progression of the disease, the psyche remains remarkably clear.

CESSATION OF REPEATED PULMONARY INFARCTION AND OF CONGESTIVE FAILURE AFTER TERMINATION OF AURICULAR FIBRILLATION BY QUINIDINE THERAPY

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Marked congestive failure, serious organic heart disease, active rheumatic infection and evidence of embolism are generally, and quite correctly, regarded as contraindicating the use of quinidine in the treatment of patients with auricular fibrillation. In the cases described below, the administration of quinidine was undertaken despite these generally accepted contraindications and was followed by abrupt and striking clinical improvement with return to normal rhythm. In one case the improvement has persisted to the time of writing and in the other, in which quinidine was probably life-saving at the moment, the patient survived nearly three years before eventual death from his circulatory disease.

CASE REPORTS

Case 1. History (Adm. 29019). B. C., an American housewife, 49 years of age, entered the Beth Israel Hospital on November 6, 1935, because of breathlessness, pain in the chest, jaundice and swelling of the legs.

Her father had died of "heart trouble" at the age of 68; one brother, 51, was known to have had rheumatic heart disease during the preceding 15 years.

Nine years before entry to the hospital, the patient, shortly after attempting to lose weight by diet and thyroid, noted the onset of redness, tenderness and swelling of various joints. This migratory polyarthritis persisted for approximately three months. During approximately five years before entry to the hospital, she occasionally suffered from attacks of paroxysmal nocturnal dyspnea and on several occasions noted swelling of the lower extremities. Ten weeks before entry, the patient felt cold and "grippy," developed a sore throat and soon thereafter noted pain, redness and swelling of various joints similar to that present nine years previously. Along with persistence of pain, redness and tenderness of the joints, the patient showed progressively higher temperature, ranging from 101° to 103°F., became more dyspneic and suffered from occasional attacks of breathlessness, accompanied by sharp pains in the chest aggravated on inspiration, orthopnea, marked palpitation, and cough productive of sputum, occasionally blood tinged. From time to time during this illness, the cardiac rhythm was absolutely irregular for periods lasting several hours to a day.

Examination. The patient appeared seriously ill. She was orthopneic; the skin was warm and moist. Respirations were shallow, labored and rapid. Examination of the eyes, ears, nose, mouth and neck revealed no abnormalities, except venous engorgement of the jugular veins and icteric sclerae and skin. Examination of the chest showed dullness at both bases posteriorly. A pronounced friction rub was heard

at the left base anteriorly and at the left axilla. Numerous moist râles were audible at both bases. The heart was moderately enlarged. At the apex the first sound was snapping, followed by a moderately rough systolic murmur and a rumbling mid-diastolic murmur. A diastolic murmur, decrescendo in character, was heard following the second aortic sound and was loudest at the third interspace immediately to the left of the sternum. The blood pressure was 110 systolic and 70 diastolic. At the time of admission the heart was regular in rhythm. Examination of the abdomen was unsatisfactory: no abnormal masses were palpable. Moderate pitting edema of both legs was present, extending up to the knees. The temperature on admission was 102.2°F., the heart rate was 104 and respirations were 43 per minute.

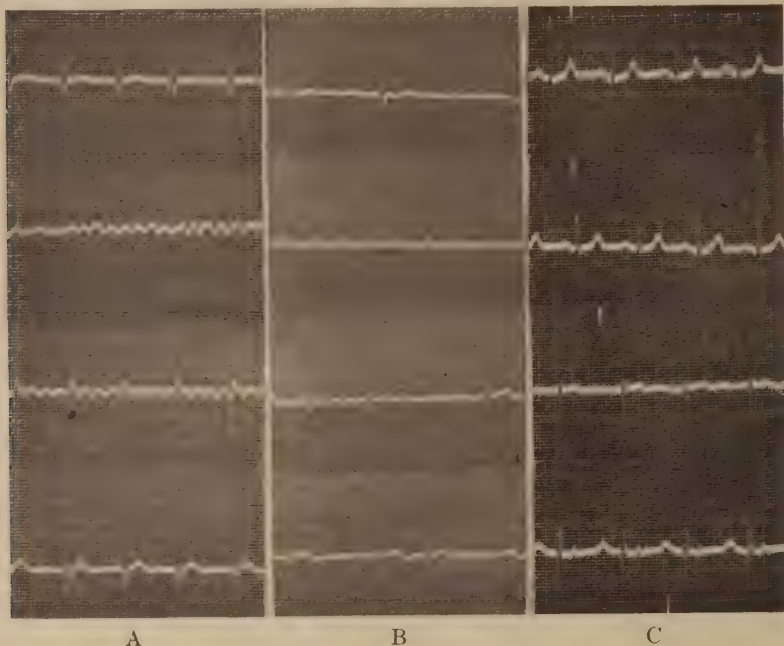


FIG. 1. A) Electrocardiogram of Case 1, B. C., November 15, 1935, showing auricular flutter with 4:1 block. Auricular rate, 332; ventricular rate, 83. Note the wide S waves in Lead I in this and the succeeding two figures (indicative of bundle branch block). Lead IV has polarity the reverse of the present rule.

B) Electrocardiogram of B. C., November 16, 1935, showing auricular fibrillation with ectopic ventricular beat in Lead III.

C) Electrocardiogram of B. C., November 3, 1936, showing normal rhythm, rate 80, and normal auriculoventricular conduction.

Laboratory Data. The red blood count was 4,210,000; the white blood count was 17,850; the hemoglobin was 70 per cent. There were 78 per cent polymorphonuclear leucocytes, 18 per cent lymphocytes, and 4 per cent large lymphocytes. Examination of the smear showed moderate changes in size and shape of the red blood cells. Examination of the urine revealed a very slight trace of albumin and a slightest possible trace of bile, no red blood cells, no sugar. Examination of the blood showed an icteric index of 20; a quantitative Van den Bergh showed 2.4 mg. per 100 cc.

The diagnoses were active rheumatic fever; rheumatic heart disease with mitral stenosis and aortic regurgitation; paroxysmal auricular fibrillation; pulmonary infarction; congestive heart failure.

Course. During the first two weeks of the patient's stay in the hospital, the clinical course was stormy. Auricular fibrillation became established instead of being intermittent. An abscess which had developed from the previous hypodermic injection was drained on the fourth hospital day, but the patient's temperature continued to be elevated to approximately 102.6°F. Respirations were labored. Icterus became more pronounced and almost every day the patient had episodes of severe, stabbing pain in various parts of the chest and raised sputum which was occasionally bloody. Friction rubs were heard from time to time. Evidences of congestive failure increased. X-ray examinations of the chest showed changes consistent with pulmonary infarction.

The increased jaundice and evidences of congestive failure, together with the findings on physical examination, indicated that the patient's condition was critical and the prognosis poor. It was felt that the repeated pulmonary infarcts were largely responsible for the progressive downward course. Electrocardiographic tracings taken before the administration of quinidine at times showed auricular flutter, 4:1 block, with auricular rate of 332 and ventricular rate of 83 (fig. 1A), and at times auricular fibrillation (fig. 1B). It was realized that the chances for the patient's recovery were slight, but that it might be possible to avert further pulmonary infarction by restoring the patient's heart to regular sinus rhythm by the administration of quinidine. The danger of loosening thrombi by such action was clearly recognized and the dangers, as well as the possible benefit, were explained to the family. With the consent of the family, quinidine was administered on November 18, 1935, in doses of three grains every six hours, and then three grains every four hours. Digitalis in doses of 0.1 or 0.2 grams daily had been given during the preceding twelve days and was continued. The auricular fibrillation ceased on the first day of treatment with quinidine, and the clinical course became more favorable. Further evidences of pulmonary infarction no longer appeared. Except for three days in which the temperature rose to 101°F. and at one time to 103°F., the patient made an uneventful convalescence. Evidences of congestive failure gradually subsided and she was discharged on December 15, 1935, quinidine having been discontinued five days previously.

From that time until the present, approximately five and one-half years, the patient has felt entirely well, has been ambulatory, has maintained normal sinus rhythm (fig. 1C) has had no recurrence of acute rheumatic fever and leads a life somewhat restricted but active, avoiding any strenuous exertion.

Case 2. History. J. L., a schoolboy, 19 years old, entered the Massachusetts General Hospital on February 28, 1935, for the treatment of uncontrolled tachycardia (rate 150), absolute cardiac arrhythmia and congestive failure (as shown by orthopnea, increased jugular pulse and engorged liver), apparently set off by rheumatic fever complicating chronic rheumatic heart disease with marked cardiac enlargement, aortic regurgitation and mitral stenosis and regurgitation.

He had rheumatic fever for the first time in the late fall of 1924 when he was nine years old and because of the persistence of this infection he visited the Children's Heart Clinic of the Out-Patient Department of the Massachusetts General Hospital in the late spring of 1925. For nearly two years he had almost continuously active rheumatism; for part of the rest-treatment he spent five months at the House of the Good Samaritan in the fall and winter of 1925 to 1926. The infection left him with a badly damaged heart, but from 1926 to 1934 he was in a fair state of health, attending school and quietly active without symptoms.

In November, 1934, he had a mild respiratory infection following which he began to suffer from palpitation consisting of frequent bouts of irregular racing of his heart.

Digitalis therapy was started and continued in the dosage of $1\frac{1}{2}$ to 3 grains daily. Nausea and vomiting occurred occasionally and early in December he coughed up about half an ounce of bright red blood; two weeks later there was a similar small hemoptysis. For the next two months he lived a miserable existence, much of the time in bed, troubled chiefly by the palpitation which finally became continuous for some weeks before hospital admission on February 28, 1935. He also suffered from weakness, an upset stomach and frequent orthopnea. In January, because of the very rapid heart rate (160 to 180), 6.0 cc. of digalen were given intravenously and repeated; the heart rate dropped temporarily, but vomiting ensued, the drug had to be stopped for a while, and the heart rate rose quickly again, auricular fibrillation persisting.

Examination. He had a mouth temperature of 100.8°F. , an irregular heart rate of about 150, and a respiratory rate of 26 per minute. The cardiac apex impulse was

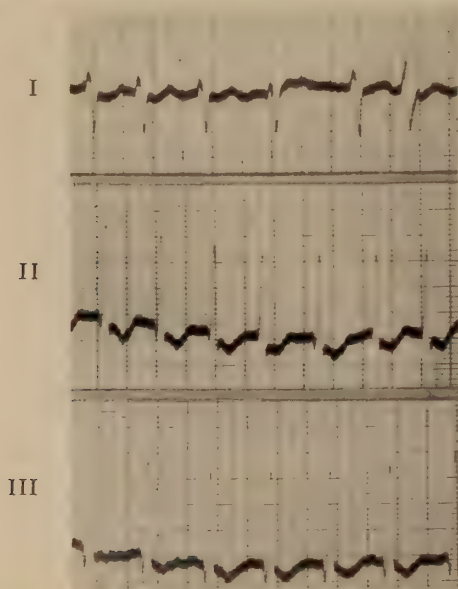


FIG. 2. Electrocardiogram of J. L., March 1, 1935 showing auricular fibrillation with uncontrolled ventricular rate averaging 155, right axis deviation, with sagging S-T segments in Lead I, and inverted T waves in Leads II and III. Time equals 0.2 and 0.1 second.

forceful and tumultuous in the seventh intercostal space, mid-axillary line. There were loud aortic systolic and diastolic murmurs and moderately loud mitral systolic and mid-diastolic murmurs. The blood pressure was 154 systolic and 20 diastolic. The jugular pulse was increased. The lungs were clear. The liver was enlarged (the tender edge felt three finger-breadths below the costal border). There was no edema of the legs or clubbing of the fingers. No rheumatic nodules were found.

Laboratory data showed leucocytosis (at first 21,400, dropping after a few days to 18,540 and again in another week to 11,400), normal red blood cell count (5.2 million) and hemoglobin (80 per cent), rapid sedimentation rate, normal urine and stools, negative Hinton reaction, normal basal metabolic rates (repeated several times), and auricular fibrillation by electrocardiogram (fig. 2).

We expressed the following opinion at that time: "The problem is that of control of the ventricular rate which has responded little or not at all to large doses of digi-

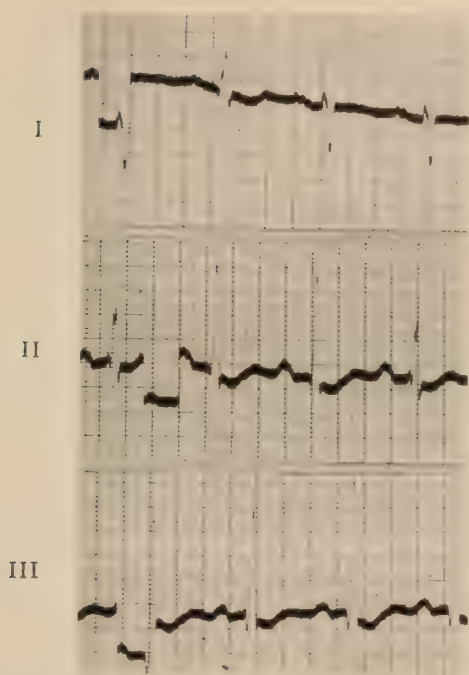


FIG. 3. Electrocardiogram of J. L., March 3, 1935, showing normal rhythm with prolonged P-R intervals at a heart rate of 80 with slightly aberrant or very late premature ventricular complexes every third beat in Leads I and II, moderate right axis deviation with low T₁, and diphasic T₂ and T₃. Record of standardization is shown at the left of each lead.

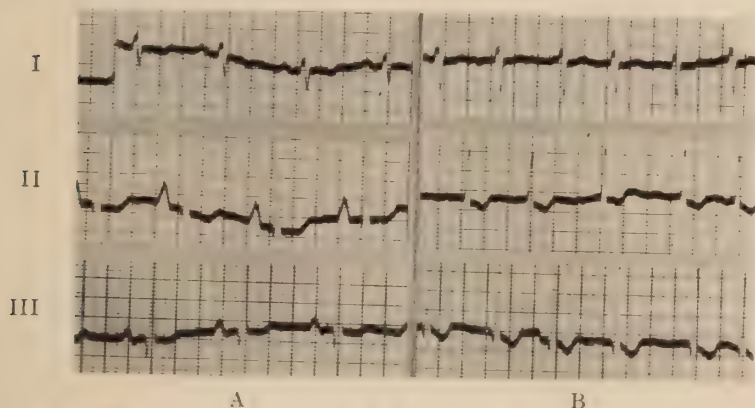


FIG. 4. A) Electrocardiogram of J. L., December 20, 1935, showing normal rhythm at a rate of 80, right axis deviation, and large P waves in Leads II and III.

B) Electrocardiogram of J. L., December 20, 1937, showing a return to auricular fibrillation but with a fairly well controlled ventricular rate averaging about 100.

talis at home. Also quinidine in small to moderate dosage was ineffective at home. He has been referred to the hospital for further trial of quinidine in larger dosage or

more effective digitalization or both. It is difficult to know whether he has had too much digitalis or not—his nausea and inverted T waves (of electrocardiogram) suggest that he has digitalis intoxication. On the other hand, some of the nausea may be due to his gastrointestinal and hepatic congestion. I would advise quinidine sulphate six grains every two hours for five to seven doses daily for a few days until normal rhythm is restored, 'toxic' signs appear, or failure of this therapy is evident. It will be as well to omit the digitalis for a day or two during the quinidine therapy. Why the heart rate is so high and uncontrollable is not clear, but active rheumatic infection may explain it (he has leucocytosis and some fever)."

Course. On the day of entrance to the hospital, he received six grains of digitalis without any beneficial effect. The next day, March 1, and again on March 2, he received 30 grains of quinidine sulphate in five doses of six grains each (at two hour intervals) each day.

On March 3 he showed normal rhythm at a heart rate of 90, interrupted by frequent late ventricular premature beats (fig. 3). The P-R interval was prolonged (0.22 second). There was moderate right axis deviation by electrocardiogram, with low T waves in Lead I, diphasic T waves in Lead II, and inverted T waves in Lead III.

He at once felt much more comfortable, and within a few days practically all his symptoms had subsided along with the evidence of his congestive failure, although active rheumatism was thought still to be present. He was discharged home, greatly improved, on March 17, 1935, to continue rest-treatment and daily rations of quinidine sulphate (3 grains four times daily) and of digitalis (1½ grains once daily).

The normal heart rhythm persisted (fig. 4A), except for occasional short paroxysms of tachycardia, until 1937 despite the occurrence of left hemiplegia, due doubtless to cerebral embolism, in December, 1935. He was left with a paralyzed left hand.

Auricular fibrillation recurred during the summer of 1937, over two years following its abolition by quinidine; it persisted thereafter, but in the absence of active rheumatism the heart rate was fairly well controlled by digitalis (fig. 4B).

Early in November, 1937, when he was nearly 22 years old, he caught cold; a few weeks later he began to be troubled by dyspnea and for the first time by edema of the ankles. He reentered the hospital on December 18, 1937, with congestive heart failure, doubtless precipitated by active rheumatism. Six days later, while apparently improving, he was suddenly taken seriously ill with some complication, the nature of which was not clear but which was thought to have been mesenteric embolism because of the onset with severe pain in the region of the umbilicus. Fever, tachycardia and coma quickly developed and he died the next day. Permission for autopsy was not obtainable.

DISCUSSION

The striking, if not unique, experience exemplified by the first case serves to emphasize certain general considerations which are of clinical interest. The frequency of pulmonary embolism and infarction is evidently greater than was formerly appreciated (3); cases similar to ours may be encountered more frequently in the future.

The hazard of employing quinidine under such circumstances, while definite, cannot be accurately evaluated. Dr. B. S. Oppenheimer, it is pleasant to recall, in his paper on "Results with Quinidine in Heart Disease," stated in 1922 (1):

"... we think that the increased danger from embolism during the transition from fibrillation to coordinate auricular contractions has been somewhat exaggerated.

During the course of auricular fibrillation, embolic phenomena, more particularly cerebral embolism, are not rare. Indeed, we have had two patients who during the course of auricular fibrillation had hemiplegia apparently due to emboli; but both subsequently responded to quinidine by a change to sinus rhythm without suffering from a recurrence of symptoms of embolism, either during or after the transition."

Other authors (4, 5, 6, 7) have in the years since 1922 administered quinidine to patients with previous cerebral, brachial or femoral emboli without precipitating fresh embolism, the patients thereafter having followed an uneventful clinical course. The situation has recently been ably summarized by Smith and Boland (4) as follows:

"It probably is not advisable to attempt to establish normal rhythm with quinidine in any case of severe congestive heart failure. There is a group, however, which we believe is an exception to this statement. In this group the patients have considerable heart disease with varying amounts of heart failure and emboli continue to form. These emboli may be cerebral, pulmonary or may occur in the peripheral vessels. In this group of cases we believe that one is justified in taking a greater risk to establish normal rhythm. The patients are less likely to have emboli if normal rhythm can be restored."¹

Sokolow (2) has recently reported a case which in certain respects is similar to ours. A middle-aged man had suffered from at least three and possibly from five peripheral emboli in the arms and legs. Three additional incidents occurred during five weeks of observation in the hospital. After weighing the risks, quinidine therapy was instituted, normal rhythm was restored, and an uneventful satisfactory course was observed for at least eight months. This led the author to conclude,

"Our experience in this case suggests that when a patient has auricular fibrillation, repeated emboli and a good myocardial function and life expectancy, serious consideration should be given to the possibility that quinidine may reestablish normal auricular activity and diminish the likelihood of further emboli. If the hazard when untreated is considerable and the benefits to be gained are many, therapeutic risk may be justifiably taken."

Our second case was of much interest also and represented a somewhat simpler and more common problem than that encountered in our first case, namely, inability to maintain myocardial sufficiency in the presence of an uncontrollable heart rate when auricular fibrillation is present. Factors of infection or infarction or of other nature which are responsible for a difficulty or impossibility of control of the ventricular rate in auricular fibrillation are also responsible for an increase in heart rate in normal rhythm, but rarely does such a heart rate run as high as that in the case of auricular fibrillation under the same stimulus (8); that was particularly true in the case we have cited above. Hence, in such an emergency as that

¹ The authors of the present paper believe that there is still another exception to the statement at the beginning of this quotation, namely when the heart rate is very rapid, as in our Case 2.

presented by our second case, it is not only justifiable but in fact even imperative to run the risk of injury by quinidine in order to restore "cardiac compensation" and perhaps to save life.

There are two other points of incidental interest in Case 2. The first is the possibility that pulmonary embolism itself occurred a few times shortly after the onset of fibrillation in the late fall of 1934, for as noted in the history, there were episodes of hemoptysis; the double argument might thus here be given for restoration of normal rhythm, namely, both that of restoring cardiac compensation and that of avoiding pulmonary embolism as in Case 1. The second point concerns the occurrence of cerebral embolism in this case when the rhythm was normal. It is, to be sure, more common to have embolic phenomena in the presence of auricular fibrillation, but in rheumatic heart disease with normal rhythm peripheral embolism is by no means rare.

Such experience as ours under circumstances where life expectancy was doubtful suggests the advisability of seriously considering the administration of quinidine, even under circumstances where the hazard is admittedly great. Under such exceptional circumstances, the prior occurrence of embolization, or of congestive failure due to uncontrolled tachycardia, may be considered indications rather than contraindications for the administration of quinidine.

SUMMARY

Dr. B. S. Oppenheimer (1), in 1922, in his paper on "Results with Quinidine in Heart Disease," described his experience with two patients who, during the course of auricular fibrillation, had hemiplegia due to emboli. Both subsequently responded to quinidine by a change to sinus rhythm without suffering from a recurrence of symptoms of embolism, either during or after the treatment.

In further development of this same theme, we have herewith reported two patients in whom the administration of quinidine with consequent return to normal rhythm was undertaken despite generally accepted contraindications. This was followed by abrupt and striking improvement, with cessation of pulmonary embolism in Case 1 and of congestive failure in Case 2. In Case 1 the improvement has persisted to the time of writing. In Case 2 quinidine was probably life-saving at the moment, the patient surviving nearly three years before eventual death from his circulatory disease.

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FACTORS AFFECTING THE OUTCOME IN ACUTE INFARCTION OF THE MYOCARDIUM

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Coronary disease has been a subject of keen interest to the medical profession during recent years and numerous important contributions, both clinical and experimental, have led to the most comprehensive concept that has ever existed. In spite of the advancement in the knowledge of this important disease, the interest of the physician must not become lessened, because it is only through a sustained interest and an enduring inquisitiveness that constructive supplements to our knowledge of coronary disease will be made. Nevertheless imponderables still exist and among them are certain unknown factors which determine recovery or death in acute infarction of the myocardium. However, some knowledge regarding this important phase of the problem has been acquired and a consideration of the known facts seems appropriate.

Acute infarction of the myocardium may occur in several ways: (a) from thrombotic occlusion of a coronary artery or arterial tributary involved and usually narrowed by arteriosclerosis, (b) from the rupture of a subintimal arteriosclerotic abscess with the discharge of lipoid material into the lumen of the vessel, (c) from intramural hemorrhage in an arteriosclerotic coronary artery resulting in complete closure of the vessel with or without secondary thrombosis, and (d) less commonly from an embolus.

Under the first three circumstances the sudden closure of the artery has been preceded by arteriosclerosis and usually by similar involvement of other tributaries of the coronary arterial tree. Here, arterial narrowing has occurred in one or more regions, which may be localized to a small portion of a vessel or may encroach on the lumen for a considerable distance.

COLLATERAL CIRCULATION

The element of time is an important determinant in recovery or death when arterial closure supervenes. When the obliterative process has been gradual, the heart frequently is enabled to create channels of collateral circulation, at times, quite adequately serving as a by-pass to the region or regions where arterial obliteration impends. This process has been demonstrated clearly in the human heart by Blumgart and his co-workers (2, 3) and independently by R. L. Smith (5) of the Mayo Foundation, by injection methods, using a fluid medium permitting the demonstration of minute arterial tributaries. These studies demonstrated

anastomotic communications of a diameter of less than 40 microns between various coronary arteries in some normal hearts, but these communications apparently play only a potential role in preventing the sudden and perhaps serious effects of coronary narrowing or closure. In hearts in which marked narrowing or closure of coronary arterial tributaries occurs, collateral circulation may be present and intercommunicating vessels measuring up to 200 microns were found to exist. Such collateral channels are capable of compensating for the reduced vascularity resulting from arteriosclerotic narrowing or actual occlusion of main coronary arteries so that the blood supply to the heart remains relatively adequate for a restricted mode of life. Time is required for this process to develop and this less appreciated mechanism of repair always must be borne in mind when the convalescent course of a patient is planned. It is not a matter of weeks, but rather one of months and years.

In some cases, pre-existing collateral circulation was found to be so extensive and adequate that the myocardium escaped acute infarction when complete arterial closure eventually supervened. The collateral vessels frequently bridge the gap between neighboring tributaries and at times are distributed so extensively as to permit communication between arteries of the right and left ventricles.

The failure of the establishment of some degree of collateral circulation obviously diminishes the chance of the patients' recovery when arterial closure occurs, and likewise predisposes to a more widespread area of myocardial destruction.

THE ACUTE INFARCT

The extent and the depth of the infarct are important in their relation to recovery or death because it is evident that, when a large region of myocardium has been destroyed, the chances for effective healing become reduced. Even in instances in which the patient survives the immediate hazards of abrupt closure of a coronary artery and healing of the infarct occurs, the resulting fibrosis may be so extensive as greatly and permanently to impair the functional efficiency of the heart, heralding early and refractory congestive heart failure, with or without the development of ventricular aneurysm.

When the infarct penetrates deeply into the myocardium and involves the subendocardial myocardium, intraventricular thrombosis occurs particularly when the apical region of the ventricle is involved. This status engenders serious complications in the form of fatal or permanently disabling arterial emboli. When the infarct extends toward the surface of the myocardium, pericarditis develops, a complication which is, fortunately, usually compatible with recovery.

It must always be borne in mind that two arteries may become occluded during what appears to be one episode, or two closely related attacks may

be interpreted as indicating first partial and then complete closure of a single vessel. Under these circumstances serial electrocardiograms usually permit the recognition of the two infarcts.

Various opinions have been expressed regarding the location of the infarct in relation to recovery. In a previous study I reported the findings in a representative series of cases of acute myocardial infarction and did not find any significant difference in the mortality rates of patients who had infarcts situated in the anterior or posterior walls of the left ventricle. This observation has been confirmed again by Woods. He has added a very significant finding by the demonstration that, when the electrocardiogram fails to permit the localization of the infarct, in the majority of the cases the interventricular septum participated in the infarction process. The cardiac mortality rate is extremely high in this specific group of cases.

Another factor enters into the consideration of acute infarction of the myocardium, one that may influence, not only the severity and the duration of the painful seizure, but also the extent of the infarcted region. This factor is vascular spasm, not of the larger arteriosclerotic arteries but rather of the smaller arteries and arterioles of neighboring vessels or anastomoses. The factor of spasm combined with inadequate pre-existing collateral circulation or the complete absence of the latter may be an important influence in preventing the healing of infarcts. Those instances of progressive myocardial necrosis in which spontaneous rupture of the heart occurs with fatal hemorrhage are well known, though fortunately not common.

Owing to its direct bearing on clinical judgment in acute infarction of the myocardium it seems appropriate to discuss the healing of cardiac infarcts. The frequency with which the question is asked how long the patient should remain at complete rest in bed after sudden closure of a coronary artery testifies to the interest in and the importance of this subject. A few years ago, White and Patmos (6), investigating this subject at the Mayo Foundation, made a careful histopathologic study of cardiac infarcts which had been present from a few hours to several years. Unfortunately this work was never published and with full credit to these workers I wish to summarize the results of their investigation.

They found that, when death occurred within two to four hours after acute coronary closure, regions of focal degeneration were present in muscle of apparently normal appearance. In the muscle bundles, however, regions of early necrosis, cloudiness, pyknosis of nuclei and diminution of the transverse striations were demonstrable and there were slight interstitial edema and congestion of the blood vessels.

Infarcts from four hours to five days old exhibited necrosis and acute inflammation. The necrotic regions were found to coalesce and numerous polymorphonuclear leucocytes and extravasated erythrocytes were present.

The polymorphonuclear leucocytes first appeared within the adventitia of small blood vessels about four hours after the development of the infarct, but they gradually increased in number during the succeeding four or five days. In infarcts which were two days old, phagocytosis was well under way. The amount of fat in the necrotic and degenerated muscle cells was found to be increased and karyorrhexis and karyolysis of muscle bundles were marked. Cellular changes, ranging from hyaline to granular degeneration, occurred. Fibroblasts were observed occasionally at the margins of the necrotic portions of the infarcts which were thirty-six hours old, but they were not plentiful unless the infarcts were five days old.

Infarcts from five to twenty-two days old and even older gave evidence of rapid disappearance of the inflammatory reaction and gradual replacement by connective tissue. Fibroblasts were found to be arranged at right angles to the newly formed blood vessels and, when nine days had elapsed since the occlusive episode, they were prominent and the necrotic regions were diminished greatly. After twenty-two days regions of diffuse fibrosis were present.

In infarcts that were from three to six months old, condensation and contraction of the fibrous scar were present and represented completed healing.

More recently Mallory, White and Saleedo-Salgar (4) presented a similar investigation. The results of these studies clearly indicate the necessity and the importance of complete and prolonged rest.

There can be little doubt that the satisfactory healing of infarcts is facilitated by the establishment of collateral circulation either preceding or immediately following the sudden occlusion of a coronary artery.

ANOMALOUS CORONARY CIRCULATION

Another factor in the recovery from acute infarction of the myocardium is the fundamental architecture of the coronary arterial tree. When this is proportioned in its usual manner, a chance for recovery usually exists but, when anomalous vessel origin or distribution occurs, death may be inevitable. A comprehensive review of the literature dealing with congenital anomalies of the coronary arteries is available in a paper by Bland, White and Garland (1). For example, I have observed instances in which the entire posterior surface of the left ventricle and a portion of the apex have been supplied by a single overdeveloped branch from the right coronary artery at its bifurcation at the interventricular sulcus. The circumflex branch of the left coronary artery was absent in this case. Obstruction of this anomalous branch of the right coronary artery would affect the nutrition of the heart so extensively and profoundly that death would inevitably occur suddenly.

In other instances, a large and tortuous left circumflex branch was found to be the sole source of supply to the entire posterior and lateral

surfaces of the left ventricle. Here again, abrupt and complete closure of this vessel would lead necessarily to serious consequences. With our present methods of clinical detection, anomalous coronary circulation cannot be identified but the future of roentgenography, with safe and more effective contrast media for intra-arterial injection, may greatly expand the field of arteriography.

PROFOUND DISTURBANCES OF CARDIAC RHYTHM

The response of the heart to sudden deprivation of a portion of its blood supply is unpredictable and the many reasons for this become apparent when the preceding remarks of this discussion are recalled. Various factors undoubtedly determine the occurrence or absence of profound disturbances of cardiac rhythm, such as ventricular tachycardia, ventricular fibrillation, complete heart block and cardiac asystole.

The occurrence of complete heart block or other major disturbances in cardiac conduction usually coincides with infarction of the interventricular septum but an explanation for the other disturbances is still uncertain. Their presence or absence may not depend solely on the question of acute infarction but rather on a perilous threshold of circulatory inadequacy preceding infarction. It is a well known fact that the normal heart during the process of death is subject to a multitudinous array of disturbances of rhythm and that even here, ventricular fibrillation is a fairly common terminal mechanism. It is probable that myocardial anoxia, from whatever cause, is the prime factor in these disturbances rather than a specific set of circumstances. The occurrence of showers of premature ventricular contractions should direct attention to the possible advent of more serious disturbances of ventricular rhythm but unfortunately this phenomenon is not a positive warning.

PROMPT RECOGNITION AND TREATMENT

The prompt recognition of acute infarction of the myocardium is an important determinant in the patients' chances for recovery. Prompt recognition of the condition implies the prompt institution of management and treatment. Complete rest in bed and the introduction of measures to relieve pain and discomfort are essential. This discussion is not intended to include the treatment of coronary disease, as that is a chapter in itself. However, I cannot refrain from again emphasizing the importance and necessity of complete rest, which in the most strict sense of the term must be enforced for at least five or six weeks or more as the indications in the individual case may dictate.

And again, I wish to admonish briefly but emphatically against well intended but meddlesome treatment, which in certain instances may turn the tide of battle from victory to defeat. After the patient has been restored to a state of comfort, and provided that complications do

not occur demanding specific measures, the physician must resign himself to be a patient spectator to nature's powers of healing and repair. The tendency unfortunately exists in many quarters today for the establishment of routine treatment for various disorders. While many components of such routine programs are extremely valuable, they lose their value when indiscriminately and at times unnecessarily applied. Even the same disease in different individuals may demand differences in management and treatment. In order to maintain a safe, yet comprehensive, therapeutic philosophy, both the science and the art of medicine must be utilized wisely.

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CONCERNING THE FORM OF THE QRS DEFLECTIONS OF THE ELECTROCARDIOGRAM IN BUNDLE BRANCH BLOCK¹

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It is a great pleasure to contribute to a volume honoring one who has been a close friend for a quarter century and who has shown me many kindnesses which I remember with the deepest gratitude. It is fitting that my contribution should deal with a problem in which both of us have been deeply interested and which has been the subject of many discussions between us. These discussions and his publications have had an important influence upon my own work and that of my associates.

In 1920 Oppenheimer and Pardee (1), on the basis of a careful histologic study carried out in two fatal cases of bundle branch block, challenged the view, then generally accepted, that right branch block was represented in the electrocardiogram by diphasic ventricular complexes of the common, and left branch block by diphasic complexes of the rare kind. At that time I was firmly convinced that the accepted view which had been strongly supported by Thomas Lewis was the correct one. Dr. Oppenheimer was good enough to show me unpublished drawings of the histologic lesions in his cases, and we had several heated but friendly discussions concerning the interpretation of these lesions and the best method of finally deciding the question at issue. I recall that in the course of one of these talks he remarked, somewhat sarcastically, that if he were to convince me it would be necessary for him to cut one of the bundle branches in the living human heart. Thinking of some animal experiments done with Herrmann (2), I replied in substance that I would accept his view if stimulation of the central part of the anterior surface of the right ventricle of the exposed human heart was found to yield diphasic ventricular complexes of the kind which he attributed to left branch block. Surgical procedures involving exposure of the human heart were becoming more frequent and observations of this kind seemed not outside the range of the possible.

In the course of the next few years, one or two attempts to obtain the required data were made in my laboratory; in these we did not stimulate the heart intentionally, but tried to take advantage of the accidental stimulation of this organ incident to resection of the pericardium in constrictive pericarditis. No useful information was obtained in this way. It was not until 1929 that my associates Barker, Macleod, and Alexander

¹ Many of the observations upon which this article is based were carried out with the help of a grant from the Horace H. Rackham School of Graduate Studies.

(3) were able to carry out a well planned series of observations in which many points on the surface of the heart were stimulated electrically. Much to my surprise their observations supported the view advanced by Oppenheimer and Pardee and, on theoretical grounds, by Fahr (4) that the electrocardiograms then attributed to human right branch block really represented left branch block and *vice versa*.

These observations upon the exposed human heart had a profound influence upon subsequent studies concerned with the form of the electrocardiogram. In my own laboratory desultory observations upon precordial leads had been made from time to time from 1919 onwards (5, 6), but it was renewed interest in the bundle branch block problem that prompted us to begin in 1929 (7) an intensive investigation of their relation to direct epicardial leads and their value in the analysis of the ventricular complex.

Experiments upon dogs demonstrated (8) that unipolar² precordial leads from the extreme right side of the precordium (leads V_1 and V_2) yield QRS deflections like those inscribed in unipolar leads from the anterior surface of the exposed right ventricle, and that unipolar leads from the extreme left side of the precordium and left axilla at the level of the cardiac apex (leads V_5 and V_6) yield QRS deflections like those inscribed in unipolar leads from the antero-lateral surface of the exposed left ventricle. By means of multiple precordial leads it is, therefore, almost always possible to determine whether the epicardial surface of the human right ventricle is activated earlier or later than the epicardial surface of the left, and thus to differentiate right from left branch block with an accuracy which far surpasses that achieved by the use of limb leads alone.

A large series of cases of suspected bundle branch block in which multiple unipolar precordial leads were employed is now available. We have also performed experiments on dogs which demonstrate that, as regards the form of the QRS deflections in such leads, canine and human bundle branch block do not differ in any important respect. In right branch block, leads from the right side of the precordium (leads V_1 and V_2) almost always yield QRS complexes of the rsR' form, consisting of a small upward, a small downward, and a final large, broad, upward deflection. In left branch block, the same leads yield complexes of the rS form, in which a small upward deflection is followed by a large, broad, downward deflection. Leads from the left side of the precordium yield QRS complexes which consist of a single broad, notched R deflection in left branch block, and complexes of the qRs , or RS type in which the final deflection (S) is broad and usually notched or shurred, but not always deep, in right branch block.

² Unipolar leads are leads in which a small exploring electrode is paired with a central terminal connected through equal resistances of 5000 or more ohms to the three extremity electrodes employed in taking the standard limb leads. The deflections of such leads represent in relatively pure form the potential variations of the region upon which the exploring electrode is placed.

In both right and left branch block, the QRS complexes of the standard limb leads are far more variable in form than those of the precordial leads mentioned. The chief reason seems to be that the more common variations in the position of the heart have a much greater effect upon the former than upon the latter. It is well known that in canine branch block the QRS complexes of the limb leads are almost invariably of the concordant type in which the chief QRS deflection has the same direction in all three leads, but that in human branch block they are usually of the discordant type in which the chief QRS deflection of lead I is opposite in direction to that of lead III. This difference depends upon the circumstance that the angle made by the long axis of the heart with the long axis of the body is considerably smaller in the dog than in most men and women with hypertensive or arteriosclerotic heart disease. For this reason the potential variations of the dog's left ventricle are transmitted to the left hind leg. In canine branch block unipolar leads from this extremity, unipolar leads from the left side of the precordium, and leads II and III yield QRS complexes of the same sort. In human branch block, on the other hand, the potential variations of the left ventricular surface are usually transmitted to the left arm. In this case, QRS complexes of the same kind occur in unipolar left arm leads, in unipolar leads from the left side of the precordium, and in lead I. Since the left arm electrode is connected to one terminal of the electrocardiograph in taking lead I and to the opposite terminal in taking lead III the QRS deflections of one of these leads are the inverse of those of the other whenever the potential variations of the left arm are larger than those of the other extremities.

The failure of early investigators to realize that the concordance or discordance of the QRS deflections of the standard limb leads depends upon the position of the heart, and not upon some intracardiac factor, was mainly responsible for the original error in the differentiation of right from left bundle branch block. Had precordial leads been employed at the start no mistake would have been made, for, as I have already pointed out, the QRS deflections of these leads are of the same form in canine as in human branch block. Another source of the error in question lay in the emphasis placed upon the direction of the chief QRS deflection as compared to other and more fundamental aspects of the form of the QRS complex. It has been the prevailing impression that in leads I and III the QRS complexes of right branch block are almost exactly the inverse of those of left branch block. It is true that in the dog the chief QRS deflection of the standard limb leads is downward in right and upward in left branch block, but it is only in very exceptional cases that this is the sole conspicuous difference between the QRS complexes of the former and those of the latter. In left branch block the QRS complex is essentially monophasic; the broad and usually notched major component is sometimes preceded by a small deflection in the opposite direction, but this is always diminutive in comparison with its fellow. In right branch block, on the other hand, the

QRS complex is almost always definitely diphasic and often triphasic. The final broad and slurred or notched deflection is preceded by a comparatively large narrow deflection of opposite sign. The voltage of this narrow deflection is seldom less than one-fourth the voltage of its companion and frequently equals or exceeds it. In roughly half the cases a third diminutive deflection occurs at the beginning of the QRS interval.

This difference in character between the QRS complexes of left and those of right branch block is found in human as well as in canine curves and in precordial as well as in limb leads. Comparison of the precordial electrocardiograms obtained in bundle branch block with the precordial electrocardiograms of the same subject taken before the block developed or after it had disappeared suggests that it is due mainly to the difference in thickness between the lateral wall of the left ventricle and the lateral wall of the right. In bundle branch block the electric forces generated by the spread of the excitatory process through the septum from the contralateral toward the homolateral ventricle combine with the electric forces generated by its subsequent spread through the free wall of the latter to produce the final broad QRS deflection. Early in the QRS interval, the spread of this process outward through the free wall of the contralateral ventricle produces electric forces of opposite polarity. In right branch block, these forces are generated by the thick wall of the left ventricle and they are usually large enough to overbalance completely the opposed forces of septal origin and therefore inscribe a prominent early deflection opposite in sign to the final QRS component. In left branch block the forces generated by the thin free wall of the right ventricle are smaller in comparison to the forces of septal origin and the corresponding deflection is absent or inconspicuous. This situation naturally varies, of course, with the particular lead used and may be greatly altered by ventricular hypertrophy, by infarction, or by other myocardial disturbances.

In the differentiation of complete branch block from incomplete branch block and other disturbances of intraventricular conduction the most valuable criterion, when limb leads alone are available, is the length of the QRS interval. When this interval measures 0.12 second or more, the ventricular complexes of multiple precordial leads are almost always characteristic of either left or right branch block. In rare instances they are not and when this happens in cases of myocardial infarction the possibility that arborization block is present must be considered. It is also probable that a general depression of the conductivity of the specialized ventricular tissues produced by toxic agents, such as quinidin, may sometimes be responsible for a QRS interval of the length mentioned. When the QRS interval is less than 0.12 second, the QRS complexes of multiple precordial leads are not usually of the form seen in complete branch block, but they may be characteristic of right branch block when this interval is as short as 0.10 second.

When only limb leads are employed, there are only two criteria which

are of value in differentiating right branch block from left branch block. The first of these concerns the presence or absence of a conspicuous S deflection in lead I. When there is such a deflection, and the QRS interval measures 0.12 second or more, the precordial curves are, with rare exceptions, characteristic of complete right branch block. When no such deflection is present, and the QRS interval measures 0.12 second or more, the precordial leads very seldom fail to yield complexes of the kind characteristic of complete left branch block. The second criterion is based upon the general outline of the QRS complexes. If these are definitely diphasic or triphasic in those leads in which the chief deflection is of at least moderate size, right branch block is probably present; if they are monophasic or essentially monophasic left branch block is probably present. These criteria are not infallible; the first is more reliable than the second.

It was formerly thought that one kind of branch block is far less common than the other. This view was based upon collections of electrocardiograms from which those of the kind obtained in the majority of the cases of right branch block were excluded, apparently because of the notion that right and left branch block should produce discordant complexes of exactly opposite kinds. Actually, right branch block is nearly or quite as common as left, but the classic curves which have been considered characteristic of bundle branch block of the rare kind are very uncommon. Such electrocardiograms display a broad S deflection in lead I, but the QRS complexes are essentially monophasic. Multiple precordial leads have been taken in only a small number of cases in which the standard electrocardiogram was of this kind. In the majority of these, the precordial electrocardiograms were characteristic of right branch block, but in several instances they were characteristic of left branch block.

The patient whose electrocardiograms are shown in figure 1 was a man, aged 56 years, with high-grade cardiac failure, great enlargement of the heart, arterial hypertension (blood pressure 180 systolic and 120 diastolic), and general arteriosclerosis. His weight was 113 pounds and his height 62.5 inches. Precordial leads were taken on two occasions and on both all of the features commonly seen in left branch block were present. The form of the standard electrocardiogram was somewhat variable, but the first set of curves displays nearly monophasic discordant QRS complexes of the rare kind. The corresponding unipolar limb leads show that the potential variations of the right arm (lead V_R) were small, that those of the left arm (lead V_L) were similar to those of the right side of the precordium (leads V_1 and V_2), and that those of the left leg (lead V_F) were similar to those of the left side of the precordium (lead V_6). It is apparent that in this instance the position of the heart was such that the potential variations of the right ventricular surface were transmitted to the left arm and the potential variations of the left ventricular surface, to the left leg. For the sake of brevity, we may say that the heart was in the "vertical" position,

but it may well be that, in bringing about the situation in question, rotation of this organ about its long axis plays a more important role than a decrease in the angle made by this axis with the long axis of the body.

We have not seen an unquestionable example of right bundle branch block in which the standard limb leads displayed essentially monophasic discordant complexes of exactly the kind usually seen in left branch block. In a few instances, however, we have encountered discordant curves of the kind illustrated in figure 2. The patient whose electrocardiograms are reproduced in this figure was a man, aged 62 years, whose chief symptoms were due to a duodenal stricture. Examination revealed general arteriosclerosis, but the heart was not enlarged and no valve lesions were present.

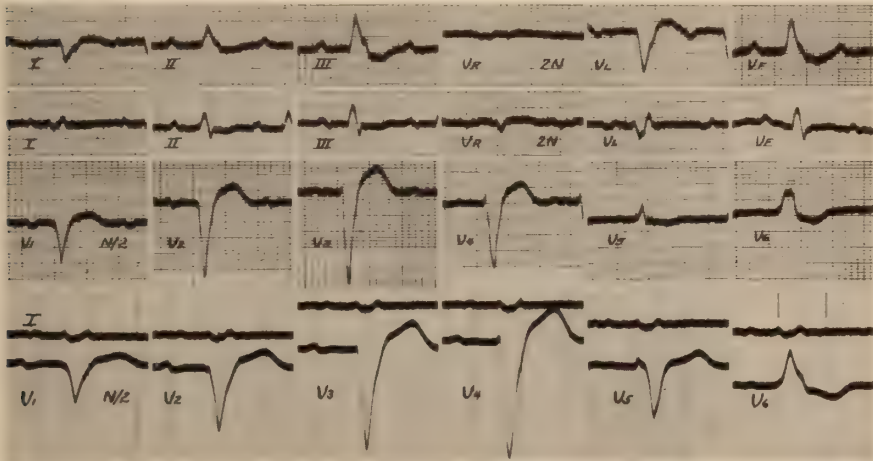


FIG. 1. The standard limb leads, unipolar limb leads (V_R , V_L and V_F) and unipolar precordial leads obtained in Case 1. The first set of extremity leads was taken on February 28, 1941, the second set on March 14, 1941. The first set of precordial leads was taken on March 4, 1941, and the second set on March 14, 1941. The precordial leads were taken with the galvanometer at one-half the usual sensitivity. The potential variations of the left arm (V_L) are like those of the right side of the precordium (V_1 and V_2); the potential variations of the left leg (V_F) are like those of the left side of the precordium (V_6). The precordial leads show that left branch block is present.

The blood pressure was normal. The QRS complexes of the first two precordial leads (V_1 and V_2) are of the kind usually seen in the right branch block. Those of the last two precordial leads are not, for the R deflection is not only very small when considered alone, but it is very small in comparison with the S deflection, so that these complexes have an essentially monophasic outline. In this instance, no unipolar limb leads were taken, but since the QRS deflections of the leads from the left side of the precordium clearly resemble those of leads II and III it is obvious that the potential variations of the left ventricular surface were transmitted to the left leg. Since the QRS complexes of leads I and II are of opposite form the potential variations of the right arm were evidently small. Finally,

since the QRS complexes of the limb leads are discordant, and since, at any given instant the sum of the potentials of the three extremities must be zero, it is clear that the potential variations of the left arm were opposite in character to those of the left leg and would have inscribed in a unipolar lead QRS deflections like those of lead I and the leads from the right side of the precordium. It is apparent, therefore, that the potential variations of the right ventricular surface were transmitted to the left arm and that in this instance also the heart was in the "vertical" position. In lead I, the QRS complex is triphasic and displays Q and S components. These deflections are both rare in this lead in left branch block, and the correct diagnosis could have been made in this case without recourse to multiple precordial leads. The standard electrocardiograms reproduced in figure 1,

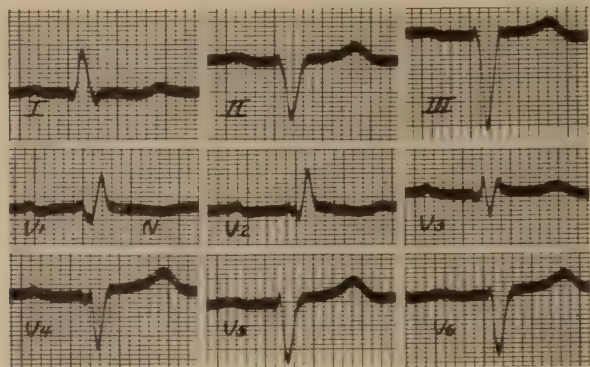


FIG. 2. The standard limb leads and unipolar precordial leads obtained in Case 2. The ventricular complexes of the latter indicate that right bundle branch block is present. The QRS deflections of the leads from the left side of the precordium (V_5 and V_6) are like those of leads II and III.

on the other hand, afford no reliable clue which would have made this possible.

In some cases of human branch block, the heart is in a position similar to that of the dog's heart. For the sake of brevity, we may call this the "semi-vertical" position. Although the potential variations of the left ventricular surface are transmitted to the left leg, those of the right ventricular surface are not transmitted to the left arm, as in the "vertical" position, and unipolar leads from this extremity yield small QRS deflections of variable outline. The QRS complexes of the standard limb leads are concordant and resemble those seen in canine branch block except that in right branch block the narrow R waves are usually larger in comparison to the broad S waves.

As indicated in a previous paragraph, the potential variations of the left ventricular surface are transmitted to the left arm in the vast majority

of the cases of human branch block. The potential variations of the left leg are then like those of the right ventricular surface ("horizontal" position) or small and of variable outline ("semi-horizontal" position). In either case, the QRS complexes of the limb leads are discordant and of the kinds with which we are most familiar. When the QRS interval is abnormally long but the QRS pattern unfamiliar, precordial leads are often necessary to differentiate between bundle branch block and other defects in intraventricular conduction and to determine whether the conduction defect is on the right side or on the left.

SUMMARY

Multiple unipolar precordial leads have been employed in a large series of cases in which bundle branch block was thought to be present. In the vast majority of instances the use of such leads made it possible to determine whether bundle branch block was present, and if so, whether the conduction defect was in the right or in the left bundle branch.

A diagnosis of complete bundle branch block should not be based upon the limb leads alone when the QRS interval measures appreciably less than 0.12 second. When the QRS interval equals or exceeds this value, the presence of a conspicuous S deflection in lead I indicates that the conduction defect is on the right side. The absence of such a deflection indicates that the conduction defect is on the left side.

The position of the heart has a profound influence upon the form of the QRS complex in limb leads. In bundle branch block, the human heart is usually in such a position that the potential variations of the left arm resemble those of the left ventricular surface while the potential variations of the left leg are either small or like those of the right ventricular surface. When the position of the heart is such that these relations are reversed, left branch block may be mistaken for right branch block and *vice versa* if precordial leads are not taken.

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ULCER IN MECKEL'S DIVERTICULUM. UNUSUAL ROENT- GENOLOGIC FINDINGS

CASE REPORT

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INTRODUCTION

A Meckel's diverticulum results when the embryonal yolk stalk between the alimentary canal and the yolk sac is incompletely obliterated so that the distal end remains open. It occurs in 2 per cent of adults; it is three times more frequent in males; and is located about 40 inches from the ileocecal valve in the ileum. In addition to obstruction, inflammation, and tumor formation, it gives rise, due to the frequent presence (16 per cent) of ectopic islets of gastric mucosa, to the occurrence of peptic ulcer in the diverticulum. These ulcers occur chiefly in young individuals and are characterized by vague lower abdominal pains and chiefly by massive intestinal hemorrhages. Perforation occurs not infrequently. It is not our intention to describe these ulcers in detail. The reader is referred to the paper of Aschner and Karelitz wherein the subject is fully discussed (1). It should be mentioned, however, that the occurrence of these ulcers next to heterotopic gastric mucosa in a Meckel's diverticulum is often adduced as a strong argument in favor of the importance of the acid-peptic factor in the mechanism of ulcer production.

The case described herein is presented because of the following unusual features: 1) A pre-operative diagnosis was made clinically by two independent observers; 2) there was the unique finding of the diverticulum roentgenologically with the appearance of a lesion in it; while Meckel's diverticulum has been seen and reported radiographically in a few cases, actually 7 cases in the literature (2), to my knowledge, this is the first case in which an abnormality in the diverticulum was demonstrated; 3) a healed and open ulcer was found in the diverticulum resected by the surgeon.

CASE REPORT

History (Adm. 375988). The patient, a boy of 16, was first seen 2½ weeks after a moderately severe intestinal hemorrhage. Six months previously he had been admitted to another hospital because of the passage of a large amount of bright red blood from the rectum associated with fainting. He received several transfusions there and made an uneventful recovery. Gastrointestinal radiography and sigmoidoscopy were reported as negative. The case was considered one of a "silent" duodenal ulcer. He remained well until the second hemorrhage mentioned above.

This time the hemorrhage was less severe and his hemoglobin fell only to 70 per cent. The patient was referred to me for opinion by Dr. Benjamin Sacks who suspected an ulcer in a Meckel's diverticulum. This was also my independent impression, reserving the possibility of a bleeding rectal polyp. Sigmoidoscopy, however, was negative. He was then referred to the medical ward of Dr. B. S. Oppenheimer at The Mount Sinai Hospital for further studies. A gastrointestinal series revealed at the two hour observation, before any barium had reached the cecum, a peculiar finger-like projection pointing downward and to the left with an irregular filling defect in its tip (fig. 1). This was considered somewhat suspicious but not definite

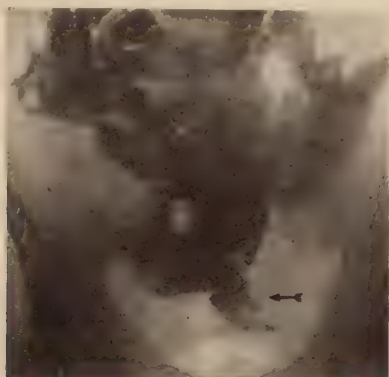


FIG. 1. Radiograph taken two hours after barium meal. No barium has reached the cecum. Diverticulum projects downward and has a filling defect in its tip and two lateral incisures (site of the ulcers).

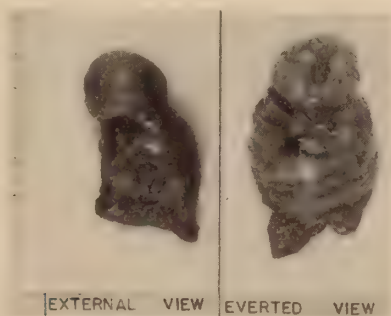


FIG. 2. Two photographs of the resected specimen. The everted view reveals the ectopic mushroom of gastric mucosa at the tip. One centimeter proximal there is an open ulcer and next to it the scar of a healed ulcer.

enough for a positive diagnosis. He was, therefore, discharged from the hospital. A second x-ray examination in my office revealed the same peculiar loop seen in the hospital radiographs. Again the filling defect was noted in the tip. There were also two spastic incisures in the contour of the loop. He was readmitted to the hospital and operated upon by Dr. Harold Neuhof. At a site in the ileum $2\frac{1}{2}$ feet proximal to the ileo-cecal valve, a rather large Meckel's diverticulum was found and resected. In its tip was an elevated mushroom-like mass of tissue with a small sinus in its center. This led into another small mass of glandular tissue at the tip of the structure. The tissue at the tip was identified histologically as a small piece of

pancreas whereas the large mushroom piece was typical gastric fundus secretory tissue. Adjacent to this ectopic gastric tissue was a depressed linear scar about $\frac{1}{2}$ inch in length and in another adjacent site was a partially healed superficial ulcer (fig. 2). These findings evidently explained the filling defect and the incisures. The patient recovered completely from the operation. He has been seen occasionally during the past $6\frac{1}{2}$ years and has remained in good health.

DISCUSSION

It is necessary to add a few words about the possibility of establishing a roentgen diagnosis of a Meckel's diverticulum with or without an ulcer in it. After the ingestion of the barium, careful studies of the small intestines 2, 3, 4 and 6 hours later may reveal the diverticulum. It appears as a dense, rounded, half-moon or finger-like projection from a loop of terminal ileum. It may be very difficult to recognize. In a case operated on for subacute appendicitis, a Meckel's diverticulum of the finger-like variety was seen but not removed. Careful subsequent x-ray examination failed to demonstrate the diverticulum.

SUMMARY

A case of ulcer in a Meckel's diverticulum is reported because it demonstrates the possibility of diagnosing such cases clinically. An unusual radiographic picture of the diverticulum with a defect and incisures in it was obtained.

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RELATIONSHIP BETWEEN BILIARY TRACT DISEASE AND HEART DISEASE¹

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My interest in the inter-relations of the biliary tract and the heart was first stimulated over twenty years ago by that great teacher and clinician, the late Alfred Stengel. In one of his patients I observed, following operation on the gall bladder, the disappearance of auricular fibrillation; and in another the relief of severe and frequently recurring attacks of what appeared to be angina pectoris. At that time very little had been written on this subject except for Babcock's well-known paper published in 1901 (1). Breyfogle (2), however, in his recent contribution credits to Gueneau de Mussy in 1878 an observation on the association between gall bladder disease and heart disease.

In the presentation an attempt is made to discuss the subject with special attention to practical problems of diagnosis and treatment.

ETIOLOGICAL RELATIONSHIPS

In Breyfogle's paper mentioned above, the literature dealing with the co-existence of gall bladder disease and coronary disease was analyzed, and in addition new evidence bearing on the subject was presented. The data now available appears to warrant the conclusion that gall bladder disease is more common in patients who die of coronary artery disease than in control groups of patients who die from various other causes. Despite the fact that the co-existence of coronary disease and gall bladder disease is greater than can be accounted for purely on the basis of the incidence of the two diseases, necropsy data do not permit a decision among the following possibilities: 1) Does coronary disease cause biliary tract disease? 2) Does biliary tract disease cause coronary disease? 3) Does some underlying etiological factor cause both?

There is no evidence for believing that coronary artery disease causes biliary tract disease except for those disturbances which result from passive congestion in the course of coronary disease. The question whether some common etiological factor may account for the co-existence of the two diseases will probably not be answered until we have further knowledge regard-

¹ From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

ing the etiological factors concerned in the production of arteriosclerosis. It is, however, an attractive hypothesis and permits one to speculate as to whether certain metabolic faults, dietary habits, or infections may be common etiological factors in the production of both types of disease.

The evidence for the view that gall bladder disease causes coronary disease, rests almost entirely on the effects of appropriate gall bladder surgery on cardiac symptoms or behavior. It is now well known that cardiac decompensation may occasionally be relieved, various disturbances of cardiac mechanism may be abolished, and attacks of angina pectoris may disappear. In 1935 Fitz-Hugh and I (3) were able to show in patients with the anginal syndrome and marked T-wave inversions in the electrocardiogram, indicating the presence of a highly abnormal state of the myocardium, that both the angina pectoris and the electrocardiographic changes may disappear promptly after operation.

Evidence such as that cited above would seem to prove beyond question that the removal of gall bladder pathology may have a beneficial effect on the heart, but it does not bear in any way on the question whether gall bladder disease actually causes coronary disease. Although the view that gall bladder disease causes coronary disease has been attributed to Fitz-Hugh and me by subsequent writers, we were careful to make no such claim, since the evidence presented by us as well as all other evidence available does not warrant it.

The status of the etiological relationships between these two conditions may be summarized as follows: 1) Evidence indicates that gall bladder disease and coronary disease co-exist more often than would be expected from the incidence of the two diseases. 2) Removal of gall bladder disease may in some cases have a beneficial effect on the myocardium which may be shown by (a) the abolition of abnormal mechanisms, (b) restoration of compensation, (c) relief of anginal pains, and (d) disappearance of abnormalities in the electrocardiogram. 3) Nevertheless, the reason or reasons for the increased co-existence of gall bladder disease and coronary disease are as yet not established.

THE PROBLEM OF MIMICRY

Clinicians have long known that gall bladder disease may mimic heart disease and that heart disease may mimic gall bladder disease. The most important aspects of this problem may be considered under several categories.

1. *Congestion of the liver:* One of the most humiliating errors which can be made is to mistake the pain of hepatic engorgement due to heart failure for gall bladder disease. In such cases there may be pain and tenderness in the right upper quadrant. Furthermore, because of the passive congestion of the liver, Graham-Cole tests may be misinterpreted as indicating abnormal function of the gall bladder. Statements in the literature to the

effect that passive congestion of the liver must be accompanied by venous engorgement elsewhere are misleading. Although elevated venous pressure is doubtless responsible for passive congestion of the liver, the liver may still remain enlarged and tender after the increased venous pressure has subsided. At operation for supposed biliary tract disease, such patients may show only passive congestion of the liver.

2. *The anginal syndrome:* Usually there should be little difficulty in distinguishing between the pain of gall bladder colic and that of the anginal syndrome (angina pectoris or coronary occlusion). Anginal pain may extend as low as the epigastrium but it is probably never centered in the right upper quadrant of the abdomen. In the cases of angina with epigastric pain there is usually radiation upward under the sternum. Rarely anginal pain may be greatest in the chest just to the right of the sternum. Although it may radiate to the right shoulder even without radiation to the left shoulder, it does not tend to radiate to the right subscapular region. Thus pain centering in the epigastric region or right upper quadrant radiating to the right subscapular region is not anginal pain, although gall bladder disease is not the only condition which can cause such pain.

3. *Spasm in the digestive tube:* It is well known that biliary tract disease may cause spasm in various parts of the alimentary tract such as the esophagus, the pylorus, and the colon. In this connection, the recent work of Morrison and Swalm (4), is of great interest. These workers have shown that pain of the anginal type may be produced by distending the esophagus by means of a balloon. As a matter of fact, they believe that such pain is actually angina pectoris. The electrocardiograms offered as evidence to support this view do not show enough to be convincing, since slight electrocardiographic changes can be produced in a variety of ways, such as change in rate, altered position of the diaphragm, and in this instance, possibly mechanical pressure on the heart of a distended balloon in the adjacent esophagus. Edeiken (5) has reported a case in which both angina pectoris and esophageal spasm were present. In this patient, the two types of pain were so similar that the patient herself could not distinguish between them. In one type, attacks were provoked by effort and relieved by nitroglycerin. In the other, the pain due to esophageal spasm, attacks were sometimes provoked by swallowing, bore no relation to effort, and were little relieved by nitroglycerin. They could, however, be prevented by appropriate dosage of belladonna and hyoseyamus. Some workers (6) have been so impressed by the syndrome of esophageal spasm as to claim that the pains which are generally regarded as due to angina pectoris are in reality due to esophageal spasm. Concerning this view, the following may be said:

(a) There is no doubt that disturbance of the cardiac circulation occurs in connection with most attacks of angina pectoris and acute coronary occlusion. This may be shown by electrocardiograms made during and after

pain. It is true that a minority show no change even when chest leads are also made but in these it is possible that the disturbance of circulation is not great enough to produce electrocardiographic changes, or occurs in areas in which electrical phenomena are poorly reflected in electrocardiograms.

(b) The question may be raised as to the part reflex phenomena play in the anginal syndrome. It seems reasonable to suppose that the anginal syndrome may cause disturbances in the gastro-intestinal tract. Thus many patients during an attack of angina pectoris have the desire to eructate and as a matter of fact are often relieved considerably by eructation. This eructation, however, appears to originate in the stomach rather than the esophagus and the relief is in all probability due to lessened crowding of the heart during its time of distress. Various other measures which tend to lessen crowding of the heart, such as the assumption of a standing position, will often afford relief in angina pectoris. The real questions at issue are whether disturbances in the cardiac circulation will cause reflex spasm of the esophagus sufficient to cause pain and whether disturbances in the gastro-intestinal tract will cause reflex disturbances in the cardiac circulation. On these points there does not seem to be much evidence. Our data (unpublished observations) do not show that esophageal spasm causes changes in the electrocardiogram such as occur during most anginal attacks. We have a few observations which indicate that during an anginal attack there is no esophageal spasm. We feel, therefore, that the two conditions, angina pectoris and esophageal spasm, are entirely separate entities with different etiology and different mechanism but with strikingly similar symptoms.

Patients with attacks of pain due to esophageal spasm are sometimes mistakenly regarded as suffering from angina pectoris. One should hesitate to accept the diagnosis of angina pectoris even in patients with undoubted heart disease unless (a) pain is provoked by exercise and relieved by rest, or (b) electrocardiographic changes occur in association with attacks of pain. If either of these criteria is absent, other possible explanations for the pain should be sought. In a considerable proportion of cases of so-called atypical angina pectoris, the presence of localized esophageal spasm during pain can be demonstrated. Pylorospasm, as is well known, may cause epigastric and even lower substernal pain but in the absence of associated esophageal spasm or marked distention of the stomach, does not tend to produce radiation of pain to the left arm. Colonic disturbances occasionally cause precordial distress with radiation down the left arm.

The problems of mimicry mentioned above are important because of their frequency and the bearing of proper diagnosis on the future of the patient. The psychoneurotic young woman who because of some spasm in the digestive tube is labelled as having serious heart disease, can continue, so long as it is to her advantage, to remain a victim of heart disease.

The anxious breadwinner of a family, who suffers from gastro-intestinal tract spasm because he has so many worries receives an additional crushing burden when saddled with an unjustifiable diagnosis of angina pectoris. More important from the therapeutic point of view is the patient in whom the cause of the spasm and pain is unrecognized biliary tract disease. The diagnosis of angina pectoris having been made, diagnostic efforts are apt to be relaxed and no further attempt made to find gall stones, or if they are found, the patient is not operated on for fear that he is too poor a surgical risk.

4. *Acute coronary occlusion:* A vitally important problem arises when a differential diagnosis has to be made promptly between acute coronary occlusion and some surgical condition in the upper abdomen such as ruptured ulcer or gall bladder. The former demands conservative treatment and the latter may demand immediate intervention; a mistake in either direction may cost the life of the patient. One must not permit oneself to be stampeded into guessing at the diagnosis. A complete history not only of the attack itself, but also antecedent history, must be obtained; a careful physical examination made, and in case of doubt an electrocardiogram made with ordinary limb leads and no less than three chest leads with an electrode on the C_3 , C_4 , and C_5 positions. One may have to weigh carefully all the evidence in reaching a conclusion. In this connection it should be emphasized that a negative electrocardiogram is not an uncommon finding in the early stages of acute coronary occlusion.

THERAPY

The treatment of the patient with both biliary tract disease and heart disease may present difficult problems. This combination must bring to the mind of the physician the question as to what effect the biliary tract disease has on the course of the heart disease and how important it may be in provoking cardiac symptoms. Although a number of gratifying results have been reported regarding cardiac behavior following gall bladder surgery, it should be stated with emphasis that these good results are in the minority. Most patients with auricular fibrillation, heart block, or even with extrasystoles are not cured by removing the gall bladder. Cardiac decompensation is not usually cured by gall bladder surgery although shortness of breath due to flatulence may be relieved. It is only the exceptional patient with angina pectoris who is cured. Most continue to have seizures about the same grade of severity after operation as before. Most likewise continue to have the same electrocardiographic abnormalities after operation. Consequently, it scarcely seems justifiable to regard the presence of heart disease as an indication for gall bladder surgery in the hope that the cardiac condition will be improved or cured by this procedure. On the other hand, it appears that heart disease should be regarded more in the nature of a contra-indication to gall bladder surgery, rather than an

argument in favor of it, because of the added risk of operation which is considerable when serious heart disease is present. If, however, life is threatened or made miserable by biliary tract disease, which does not respond to conservative treatment, operation may properly be undertaken in spite of the presence of serious heart disease. Such patients have little to lose. If, in addition to relief from biliary tract disease, relief from the symptoms of heart disease occurs following operation, the cardiac benefit may be regarded as an unexpected extra dividend.

The views just expressed are not in accord with the opinions of many surgeons and internists. The reason for difference of opinion probably lies not in differences of results observed after biliary tract operation so much as in the criteria used for the diagnosis of heart disease, particularly angina pectoris. Relief of substernal or precordial pain after operation does not prove that the patient was cured of angina pectoris. Before arriving at such a conclusion it is necessary to distinguish between the anginal syndrome and conditions due to biliary tract disease which may mimic it, since there is a vast difference in the results to be expected in the two groups.

SUMMARY

1. Available evidence appears to indicate that the co-existence of biliary tract disease and coronary disease is significantly greater than is to be expected from the incidence of the two diseases. The cause for this co-existence is not clear. There is no good reason at present for believing that coronary disease causes biliary tract disease. Likewise, there is no valid evidence to support the view that biliary tract disease causes coronary disease. It is possible that similar metabolic faults, infections, or errors in the regimen of life may be factors in the production of both conditions but this view, however reasonable, is not as yet supported by actual evidence.

2. Biliary tract disease and heart disease may under certain circumstances mimic one another. Passive congestion of the liver may be mistaken for gall bladder disease. The anginal syndrome may be simulated by spasm of the digestive tube. It is possible that reflexes from the heart may affect the digestive tract and that reflexes from the digestive tract may affect the heart. Acute coronary occlusion and acute upper abdominal emergencies may furnish difficult problems in differential diagnosis.

3. The therapy of biliary tract disease may require modification in the direction of conservatism because of co-existing heart disease. Although cardiac symptoms may be improved following surgery on the gall bladder, such improvement occurs in only a minority of cases. Furthermore heart disease adds to the risk of operation. Consequently the presence of heart disease should be looked upon more as a contra-indication to operation than as an indication for operation. When, however, biliary tract disease threatens life or causes distressing symptoms, which cannot be controlled

by conservative treatment, it may become necessary to accept the risk of operation even in the presence of serious heart disease.

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PHYSICAL MEASURES IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE¹

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The use of physical agents, including light, heat, exercise and baths, for the improvement of the circulation of both normal and pathological states has been of recognized value since before the time of Hippocrates. The exact mechanisms were not always understood, nor can we say that we understand them thoroughly today, but clinical improvement was described by Hippocrates and later recognized and elaborated upon by Celsus, who appreciated the value of baths at the temperature of the body. He, therefore, used extensively the baths of Ragaz, Switzerland, where the temperature of the water issuing from its grand source maintains throughout the year a heat within 1°C. of the body temperature. The importance of carefully regulated heat approximating body temperature in the treatment of circulatory problems has been recently rediscovered and re-emphasized by Starr (6) and others.

Rest. Rest under proper physiological conditions must be considered a physical agent. When there is ulceration, gangrene, marked progressive discoloration, sudden local coldness or severe "rest pain," the involved extremity should be placed at relative rest. Reid (1) has demonstrated the importance of selecting the level for maintenance of the most satisfactory circulation possible under these circumstances. If the extremity is allowed to remain in a dependent position for too extensive a period of time, the veins become engorged, and this engorgement results in increased venous and capillary pressure and stagnation of blood. On the other hand, if the extremity is kept elevated, it becomes blanched and bloodless in appearance and the tissues become ischemic, because the pressure within the diseased arteries is usually insufficient to deliver fresh blood to the tips of the extremity. Such elevation, when prolonged, is known to have been a frequent cause of amputation in the past.

There is a level, between these extremes, which appears to be the most efficient from the viewpoint of a properly controlled blood supply. This is the point at which the superficial veins fill to such an extent that they project a little above the level of the skin. This will usually be found from 3 to 6 inches (7.5 to 15 cm.) below the level of the heart. Gravity assists

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the flow of arterial blood into the limb, at this level, and the blood is not hampered in its return by too greatly increased venous back pressure.

Until the lesion is healed or the acute phase is completely over, it is wise to continue the rest, after which activity should be guardedly resumed under observation until the return of the condition is considered unlikely. Specific vascular exercises should be the only exceptions allowed.

Baths. Baths, properly used, constitute a definite contribution to the treatment of occlusive vascular disease. They may be grouped as follows:

1. *Contrast baths:* The contrast bath is perhaps the most widely used bath for this type of condition. Two containers are placed side by side. These should be deep, reaching to the patient's knee. In one, water at 40.2°C . (105°F .) is placed and in the other water at "tap water temperature," 15.5 to 20.1°C . (60 to 70°F .) is used. The legs are placed first in one and then in the other at intervals varying from one to three minutes. The last immersion should always be in the hot water. Seven alternations, beginning and ending with hot water, have usually been used in our clinic. This treatment should be given once or twice a day, depending on the condition of the extremity. The theory, upon which this treatment is based, is that the patent vessels are exercised by producing alternate vasoconstriction and vasodilatation. However, there are several objections to this type of bath, which have resulted in our abandoning its use. In the first place the most satisfactory containers only reach to the knees. The blockage may be above that level so that, even though the contrast baths may produce different metabolic demands, the ability to respond may not be achieved at the level of the stimulus. Second, when previously damaged vessels are forced into sudden vasospasm, they may stay closed, which complicates the situation considerably. Third, we have found that there is often severe pain during the cold phase, perhaps due to cramping or to ischemia. Therefore, we have adopted a modified form of the long used sitz bath for this purpose.

2. *Sitz baths:* The patient sits in a tub containing at least 12 inches (30 cm.) of water at a temperature of 37.8 to 40.2°C . (100 to 105°F .) for twenty to thirty minutes at least once a day. This method overcomes all of the objections to the contrast bath. (In theory it does not exercise the small vessels as well.) The heat extends sufficiently high to activate the collateral vessels from the trunk and also the femoral arteries. No cold water is involved and, therefore, the risk of sudden permanent occlusion or of severe pain is greatly minimized. If water at this temperature seems to cause discomfort, the temperature should be reduced to 34.4 to 36.7°C . (94 to 98°F .). The technique and the temperatures used in this type of bath will be recognized as being very similar to those prescribed by Celsus at Ragaz. Of course, this type of bath is not suitable for patients who have open ulcers or gangrene, because of the risk of infection.

3. *Whirlpool baths:* If available, whirlpool baths may further stimulate

the circulation. The motion of water is especially helpful in removing the sloughs often encountered in chronic low grade ulceration. The temperature of the water should be about the same as that used in sitz baths. Whirlpool baths usually have the objection of not extending high enough on the limb.

4. *Soaks*: In our clinic we have largely abandoned wet dressings, because of their tendency to cool even under the most favorable conditions. Since this produces vasoconstriction, it does more harm than good by defeating the chief aim, that of improving the circulation to the dying cells. We have substituted in their place soaks of boric acid solution or physiologic solution of sodium chloride at 35.7 to 37.8°C. (96 to 100°F.) for ulcerated or gangrenous extremities. These may be applied two or three times daily for fifteen to thirty minutes. The foot is removed after each soak, dried carefully and placed under a warm lamp cradle at 31.2 to 34.3°C. (88 to 94°F.) to prevent chilling. The object is to allow proper drainage by softening and cleaning away crusts which tend to lock in infection, but once the infection is controlled, an attempt should be made to produce a dry lesion rather than a wet, macerated one. Healing is facilitated and the danger of infection is reduced when the lesion is dry.

Local heat. Heat is a problem of great importance in the handling of arteriosclerosis and thromboangiitis obliterans. It is probable that in the past heat has done more harm than good, because of improper use. Properly handled, it tends to reproduce normal temperature. The normal surface temperature rarely exceeds 33.8 to 35.5°C. (93 to 96°F.). In order to achieve this and hence stimulate normal metabolic processes, the temperature of the environment should approximate that level. My associates and I, therefore, use thermostatically controlled heat cradles (2) which keep the temperature between 30 and 34.2°C. (86 to 94°F.). By careful watching and the use of a thermometer an equal distance between the lamp and the extremity, it is possible to use ordinary light bulbs, but the factor of error is great and the disease in many cases has been greatly aggravated by overheating. As Starr (3) has pointed out, increasing the metabolic demands beyond the capacity of the supplying arteries, leads to increasing gangrene. Controlled heat within these limits is, in our opinion, the only safe form of heat for use in this condition. The local use of heat lamps, diathermy or short wave machines is to be condemned. I have seen in consultation many patients with severe ulceration, massive necrosis or gangrene which appeared to have been precipitated by such measures: seven of these patients lost their legs and two died, not primarily as a result of vascular disease, but rather as a result of misapplied treatment. I have emphasized this previously (4). Freeman (5) has presented experimental work which explains the mechanism for the increase in the rate of development of gangrene associated with the increase in temperature applied to the areas with impaired circulation. Since heat

produces an elevation of the metabolism of the tissues, its use to promote an increase in the circulation must be modified in accordance with the functional capacity of the vessels. In the presence of organic obstruction, the increased metabolic demands of the tissues produced by elevation in temperature may be greater than any possible improvement in the circulation. An additional source of injury, as pointed out by Starr (6) rests in the fact that the impaired blood supply cannot carry off the increased heat applied from without, so that the temperature of the tissues rises to levels which are definitely injurious.

Local heat is also of value in the treatment of thrombophlebitis. Here it is highly desirable to prevent continual venous and arterial spasms and the most satisfactory technique of which I have knowledge has been outlined by Barker (7) as follows: The entire affected limb is covered with petrolatum and a layer of gauze is applied over this. Blanket material is then soaked in hot water and wrapped around the extremity, following which a rubber sheet is applied and then hot water bottles (or a waterproof electric pad) is laid over the outside. This will often succeed in breaking a spasm of the entire vascular tree and reduce the risk of further activation of the thrombophlebitis very markedly.

Reflex heat. Using a modification of the principle employed by Gibbon and Landis (8), my associates and I have used reflex heat as a therapeutic measure as well as to determine the potential vasodilatation of the vascular tree. After trying several approaches, we have found the simplest effective technique to be merely the application of an electric heating pad over the abdomen for thirty to sixty minutes once or twice a day. Dilatation of the vessels of the extremities (considering the disease present) is thus obtained. Great heat (the maximum compatible with the safety and comfort of the patient) should be used with this device, as the dilatation occurs from the proximal toward the distal ends of the extremities. If diathermy, short wave therapy or infra-red rays are to be used for these conditions, their application should be to the trunk to produce reflex vasodilatation. For example, the maximum vasodilatation of the vessels of the lower extremities which we have observed (produced by heat) has occurred from the use of short-wave therapy over the lumbar sacral region.

Cold. Cold applications have been locally applied over small thrombophlebitic areas in the past. The trend is rather away from this practice, but there are occasional cases where the application of heat seems to result in increased inflammation and a spread of the process, which can at times be brought to a relatively abrupt cessation by the application of ice bags directly over the area involved. A protective pad should be placed between the skin and the ice bag.

Very recently experimental work has been begun with the use of ice applied to the legs with arteriosclerotic gangrene with the idea that the area of chill should be used to demarcate the point at which amputation

should be performed and that it will decrease the pain involved in amputation. I feel that this technique is, as yet, too experimental to warrant its use generally. I merely mention it as a trend.

Cold is also sometimes of value in the treatment of erythromalgia (erythromelalgia). Here the chief complaints are increased heat of the hands and feet which are often relieved by soaking in cold water. This, of course is not a cure but merely a palliative application.

Active vascular exercises. 1. *Buerger's exercises:* The exercises described by Buerger (9) have been accepted and extensively used to exercise the vascular tree, to clear away stagnant blood and to stimulate the opening of the collateral vessels.

A Modification in technique: I should like to suggest the following modification from the technique usually employed, which is based on the pathological physiology of each patient. A test should first be made to determine the time necessary to produce pallor of the affected foot by elevation. The time necessary to produce rubor on dependency should next be measured. The *times obtained* should be used in treatment, rather than any fixed schedule. For example, if pallor of a patient's foot is induced by elevation for two minutes and rubor is induced by dependency for three and a half minutes, the patient should be instructed as follows:

1. Elevate your feet at a 45° angle on pillows or an inverted chair back for two minutes.
2. Allow your feet to hang over the edge of the bed for three and a half minutes.
3. Rest them on the horizontal two to three minutes (this is an arbitrary rest period).
4. Repeat this cycle ten times two or three times a day.

The extremities may not respond in the same time periods bilaterally in which case preference should be given to the most involved limb, the one which usually responds first with both rubor and pallor. At regular intervals the timing should be re-checked and the directions to the patient modified in accordance with the results. By using this technique the production of ischemic metabolic deficits is avoided. It is important that greater attention should be paid to the temperature of the room in which these exercises are performed. If possible, it should be 26.5°C. (80°F.) or above, since the uncovering of the extremities in a cold room may produce vasoconstriction, thus cancelling any possible benefit from the exercises.

2. *Allen's exercises:* Allen (10) has suggested a modification of Buerger's procedure which is of help providing the feet are not too painful. Further exercises are performed as follows:

With the legs hanging over the edge of the bed:

1. The feet are extended downward:
2. The feet are raised by flexion at the ankle joint, not by raising the legs.

3. The toes are turned outward as far as possible.
4. The toes are turned inward as far as possible.
5. The toes are spread with the feet in normal position.
6. The toes are closed.

This should be repeated during the dependent phase of each cycle. It in no way conflicts with the above suggested modification of Buerger's exercises.

Pressure suction boot. Although variations in environmental pressure have been employed in the treatment of impaired circulation since before 1600 it remained for Landis and Gibbon (11) and Herrmann and Reid (12) to perfect a satisfactory mechanism for the use of the pressure suction boot in the treatment of peripheral vascular disease.

The principle on which the modern apparatus is established depends on the hypothesis that blood flow in an extremity can be appreciably increased by exposing the extremity to variations in pressure from positive to negative and back to positive, continuing such alternations for the duration of the treatment, which may be from one to twenty-four hours or more. The extremity is encased in a so-called boot, made of glass or metal in which the pressure changes are produced by means of connections to a properly constructed air pump apparatus. The leg is inserted in an opening which is made air tight by means of any one of a variety of types of rubber cuffs. There have been various disagreements as to the type and timing of the cycle to be used and the amounts of pressure and suction desirable. At the moment, the most extensively used cycle approximates those suggested by Herrmann and is as follows: Using atmospheric pressure as the base line, one complete cycle takes fifteen seconds. The first three second period is one of positive pressure, reaching gradually 20 mm. of mercury. Then there is a gradual downward curve, crossing the base line in the third second and proceeding to a negative pressure of minus 80 mm. of mercury at the eleventh second. A more rapid return to the base line completes the cycle in fifteen seconds. This is repeated continuously for the duration of each treatment.

In order to make this technique satisfactory in theory and practice, certain objections had to be met. To operate the boot, the cuff around the upper part of the extremity must be air tight. This produces a certain degree of constriction about the limb and thus interferes with the blood flow, especially in the superficial vessels. Several types of cuff have been devised and some have at least partially overcome this objection.

Generally, when the circulation to an extremity is increased there is an increase in the surface temperature of said extremity. At times, however, the circulation to the muscles may be increased without a corresponding surface temperature rise and vice versa. In our clinic, we have noted that the temperature of the limb is often colder after this type of treatment than before. Similar experiences have been observed in other clinics. This may be due to the above mentioned constriction or to the continuous

flow of air in and out of the boot. This observation has resulted in the use of local or reflex heat, with improvement in this regard. The amount of dilatation depends on the potential capacity of the vessels, damaged and undamaged. As is the case with all new or rediscovered methods of treatment, the first claims for this method constituted a rather optimistic picture of its value. It was stated that it was of great value for arteriosclerosis (senescent and diabetic), thromboangiitis obliterans, Raynaud's syndrome, acute embolism, frostbite and other types of circulatory impairment. Actual experience with this apparatus has greatly narrowed the indications for its use. At present it appears to be of value in selected cases of uncomplicated senescent or diabetic arteriosclerotic gangrene, acute embolism or thrombosis, if adequate surgery is not immediately available, and frostbite. I must confess that I am not absolutely convinced of its unquestioned value in certain of these conditions, although we still use it in selected cases. On the other hand, definite contraindications have been established for its use.

Pressure suction should never be employed in the presence of an acute or subacute infectious process or of any form of acute or subacute thrombophlebitis (which includes most forms of thromboangiitis obliterans) or in any cases which present evidence of autolysis of the tissues, such as cases of acute embolism or thrombosis (e.g. arteriosclerotic sudden occlusion) in which after several days the skin becomes mottled and blistered. The results of its use in these conditions may be serious. It appears futile to employ it when the level of application of the cuff is peripheral to the level of arterial blockage, yet this is constantly happening. Allen and Brown (13), Conway (14), and Wilson and Roome (15) reported unsatisfactory results in the treatment of thromboangiitis obliterans, and even Reid and Herrmann (16) have recently stated that they were no longer so enthusiastic as to the ultimate results. We do not use pressure suction therapy in the treatment of thromboangiitis obliterans, since we have observed more satisfactory results with typhoid vaccine.

Kountz (17) reported pressure suction to be of little use in experimental and clinical studies and devised an apparatus with a series of cuffs to be applied serially the length of an extremity, these being operated in sequence and tending to "milk" the blood along the limb. Increasing the temperature up to 40°C. (104°F.) increased the flow about 8 per cent in normal, but less in diseased extremities. A similar response is produced by Iontophoresis. Kountz and Smith (18) reported encouraging results with this apparatus in twenty-three cases of arteriosclerosis and thromboangiitis obliterans. Their results are difficult to interpret, however, because in addition to this mechanized treatment (a) hypertonic saline solution was given intravenously twice a week, (b) alcohol was given daily by mouth and (c) patients with thromboangiitis obliterans received typhoid vaccine intravenously.

Additional, more carefully controlled studies must be performed to

evaluate this type of equipment. I have had no personal experience with it.

Reactive hyperemia and intermittent venous occlusion. The phenomenon of "reactive hyperemia" has long been recognized. Among the early descriptions are those of Cohnheim (19) and Lister (20). The superficial manifestation is a bright flush of the skin occurring after release of a circulatory obstruction. Bier (21) observed this phenomenon for many years and developed therapeutic procedures based on the principle that obstruction and then release of the circulation would produce a marked circulatory increase and that this would be of benefit for certain pathologic states. At first it was thought that this reflex resulted from vasomotor paralysis produced by pressure of the constricting band on the nerves, but Bier demonstrated that it can occur when every connection between the limb and the body has been severed except the artery itself. (However, this apparently does not include several of the sympathetic nerves of the arterial wall.) Lewis and Grant (22) showed that hyperemia of the skin occurs on restoration of the circulation even though the cutaneous nerves have degenerated. It is impossible to differentiate anesthetic skin by its reaction from normal skin. There appears to be a reaction wholly independent not only of the central nervous system, but of the local nervous reflexes as well.

Bier (21) and Zak (23) expressed the opinion that when the circulation is occluded, the venous blood stagnating in the vessels causes them to contract and that "reactive hyperemia," which results from the release of the circulation, is a direct response of the vessels to the incoming blood.

Katzenstein (24) and Krogh (25) disagreed with this hypothesis, the latter taking exception particularly to the theory that venous blood causes vessels to constrict, while arterial blood causes them to dilate. Bier's conception depends on the supposition that the tone of the vessels is increased during occlusion and diminished when arterial blood enters them. Lewis and Grant (22) have, however, submitted evidence that this is not so and that dilatation of the vessels responsible for the cutaneous hyperemia occurs during the occlusion and not at the release.

The precise mechanism by which this takes place has been difficult to establish, involving as it probably does, complex intracellular and extracellular chemical problems. *As Roy and Brown (26) pointed out, it represents an effort on the part of tissues deprived of proper blood supply to become repossessed of it.*

The fact that hyperemia represents a phenomenon which occurs constantly, should be emphasized. The part bearing the weight of the body necessarily becomes ischemic. When one moves about shifting the weight, there is a flood of blood into the ischemic tissues compensating for the accumulated debt to local metabolism. Necrosis occurs when the weight is too steadily on certain areas, or when the vascular tree does not permit

this compensation. Instructive studies of this phenomenon as it takes place after both arterial and venous obstruction and release have been published by Lewis and Grant (22). Recent interest in the subject justifies a brief review of certain of their pertinent observations. In relation to *arterial* reactive hyperemia these authors arrived at the following conclusions:

1. Increase in the environmental temperature within certain limits produces a definite increase in response, e.g., with temperatures of 15 to 20°C. the increase in flow on release of the constriction was 2 cc. in 600 cc. of tissues, whereas at a temperature of 40°C. an identical plethysmographic experiment produced an increase of 15 to 30 cc. of blood flow per minute to 600 cc. of tissue. It is, therefore, most important that in all such studies the temperature should be carefully controlled.

2. Within certain limits, the longer the duration of occlusion, the greater is the duration of the subsequent hyperemia. The flush usually lasts approximately one-half to three-quarters as long as the preceding occlusion. Occlusion lasting more than twenty minutes is very uncomfortable, and if it lasts for hours, it may produce paralysis (27), thrombosis or other serious effects.

3. If a series of plethysmographic curves is taken in which the periods of occlusion are constant and equal to the intervening intervals, the individual curves are identical in form (only five successive curves are reported).

4. Arterial reactive hyperemia following an occlusion lasting ten minutes produces a greater effect than soaking the arm in water at 43 to 44°C. for thirty minutes. (As has been noted in this article, direct heat does not produce as great an increase in blood flow as does reflex heat (28).)

5. According to comparative studies, exercise produces an increase in blood flow which is greater in volume and duration than that produced by reactive hyperemia. In reactive hyperemia all the soft tissues seem to be affected, while in exercise the effect is mostly confined to the muscles.

In relation to *venous* reactive hyperemia the authors concluded:

1. When occlusion of the venous return flow is produced, the venous pressure within certain limits with slight variations, rises to equal the cuff pressure.

2. When the pressure is 40 to 50 mm. of mercury for two minutes or more, the pulse volume begins to increase; this becomes maximal in ten to fifteen minutes.

3. When a pressure of 20 to 30 mm. of mercury in the cuff is released the plethysmographic curve is that of a simple drop to the base line as the veins empty themselves.

4. If the cuff pressure has been higher (40 to 60 mm. of mercury) the descent of the curve is broken by a hesitation, or a secondary "hump" and reactive hyperemia occurs.

5. The size of this "hump" within certain limits, is increased by (a)

increasing the cuff pressure, (b) maintaining the cuff pressure for longer periods and (c) raising the temperature.

6. This "hump" is most probably produced by superimposed arterial active dilatation and filling to a point at which the arterial blood is entering the limb more rapidly than the veins are emptying.

7. Obliteration of the major artery supplying the limb will obliterate the hump.

8. Venous congestion carried to a high point (a pressure of 70 mm. of mercury) for five to ten minutes appears to yield a curve of vasodilatation not unlike the amplitude and duration produced by a somewhat shorter period of arterial occlusion.

9. The release of venous congestion in a normal limb is followed by flush displacing the cyanosis and varying in duration with the degree and duration of the previous congestion.

"The phenomenon of reactive hyperemia is related in its degree to one factor namely, to the blood flow debt which is usually a product of the amount by which flow is reduced and the time over which the reduction has been maintained."

Abramson and his co-workers (29) using plethysmographic machines, have recently presented further evidence confirming this observation of Lewis and Grant.

The hyperemia is a result of the active dilation of those vessels which are responsible for the color of the skin, namely the arterioles, capillaries and venules. As has been noted, the mechanism is extremely complex; the nervous reaction theory appears untenable. Other factors, such as oxygen deficiency and accumulation of carbon dioxide or of other metabolites, for instance pituitary hormones, have been studied without conclusive results.

The problem of possible therapeutic application of these principles has been emphasized by Bier and more recently by Collens and Wilensky (30) who developed an "intermittent venous hyperemia machine" capable of reproducing a cycle with the pressure and timing believed desirable.

We must consider carefully several questions in this regard. Since the phenomenon of reactive hyperemia depends on and is related directly to a receding "blood flow debt" accumulated during the period of occlusion, is it beneficial or dangerous to tissues which are barely receiving sufficient nourishment for life to go through periods of increased nutritional debt, even though the hyperemia may compensate later?

These and many other questions must be answered before the theoretic conclusions are accepted as satisfactory. Veal and McCord (31) have studied the effects of complete arterial occlusion and intermittent venous occlusion on the oxygen content of the blood with the following results: After complete arterial occlusion of the arm for five to eight minutes, followed by release, the oxygen saturation of the blood from the antecubital

vein showed a definite rise in one minute in nine of eleven cases. The saturation then decreased at varying rates. After intermittent venous occlusions, the tendency was reversed. In eight of eleven cases, there was a definite decrease in oxygen saturation of the blood at the end of one minute after release of the compressions. There was no change of significance at the end of three minutes. The point is thus brought up as to whether by "using the cycle 2:2 or 2:1 minutes" and the compression recommended (25 to 80 mm. of mercury) true reactive hyperemia is produced. Perhaps the fatigue phenomenon previously mentioned entered into these studies. No mention is made of the possibility. Allen and McKechnie (32) studied the effect of intermittent venous occlusion on the cutaneous temperature under controlled conditions. In nineteen patients (nine normal subjects and ten persons with hypertension, arthritis and peripheral vascular disease) they found no evidence that any significant or consistent vasodilatation of the vessels of the skin resulted from this procedure.

It is extremely difficult to evaluate clinically intermittent venous hyperemia or the hyperemia of Bier. It seems that Bier's hyperemia has been largely abandoned in the United States, either because of lack of conclusive therapeutic results or because more modern methods appear to offer greater promise. I have never been impressed with the clinical results of this technique in the treatment of arteriosclerosis obliterans, or thromboangiitis obliterans and have long since ceased to use it.

In all fairness we must consider that the status of intermittent venous hyperemia is not definitely established. Collens and Wilensky have repeatedly reported excellent results as following its use, but many of their patients were also treated with a routine "vascular regimen" involving abstinence from tobacco, warmth and rest (in certain cases) and these factors cloud the picture somewhat. de Takats, Hick and Coulter (33) reported favorably on the use of this technique in a series of ten cases, but their conclusions were weakened by the fact that other treatments were used simultaneously and their series was too limited in numbers to warrant the drawing of any positive conclusions.

Kramer (34), Brown and Arnott (35) and Wilson and Ogston (36) have also reported favorably on this technique.

In the vascular disease clinic and on the wards of the New York Post-Graduate Medical School and Hospital we studied and used this apparatus in twenty-three cases over a period of about one year. Occlusive conditions of varying severity were included, some advanced and severe, with gangrene; others early and less severe, without gangrene. The cuff was active on certain patients practically continuously for as long as six weeks, so that it cannot be charged that it was not given a satisfactory opportunity to show its worth. We are perfectly willing to admit the difficulty of attempting to evaluate the effects of any therapy on the course of such

conditions, but the members of our clinic were not convinced of the value of the method and in some instances it was felt to have been harmful. Therefore, it was discontinued as a routine measure.

Certain contraindications for its use became obvious: 1) a level of arterial blockage above the level of the cuff; 2) active and spreading infection of the wound, especially with streptococci or anaerobic bacteria; 3) extreme toxicity of the patient and 4) increased pain with the use of the machine. (Collens and Wilensky suggested using a 25 mm. pressure in certain cases. Lewis and Grant have shown that reactive venous hyperemia probably does not occur to any appreciable amount at this pressure).

A compression of 60 mm. of mercury and a cycle at two minutes "on" and two minutes "off" is optimal for most cases. If the patient tolerates the treatment well, it may last from one hour to several months. Reflex heat is advisable, but I do not advise the use of short wave therapy or diathermy for the involved foot as suggested by Collens and Wilensky (30).

The "vas-oscillating bed." The motor bed is a form of mechanical treatment which has recently been used in a number of clinics and was originally described by Sanders (37).

The head and feet of the patient are alternately elevated and lowered, by means of this bed, making a complete cycle taking from one to three minutes depending on the regulation of the mechanism. In this way the principle of Buerger's exercises may be continuously applied throughout the twenty-four hours. The movement is smooth; the patient soon becomes accustomed to it, and we have patients who have used these beds for as long as four years. Many of them have continued to use their beds during the sleeping hours long after their open lesions have healed. The degree of tilting and speed of the cycle can be regulated within reasonable limits. The object is to exercise the arteries, which are still able to function by producing rubor and pallor (engorgement and ischemia) as with the Buerger exercises, but continuously and without fatigue to the patient. The procedure is gentle, involves no constricting bands and appears theoretically sound, especially for the treatment of arteriosclerosis with or without gangrene. My associates and I use a thermostatically controlled cradle at 94°F. (34.2°C.) for auxiliary treatment. We have now had the opportunity to study more than one hundred cases. Clinical impressions are often deceptive guides and experimental studies are difficult to evaluate with this apparatus, but to date the workers in our clinic and in many other clinics (38) have been favorably impressed. Ulcers have been healed in certain patients in whom the pressure suction boot and reactive hyperemia machine were complete failures. Many patients who are made very uncomfortable by the action of the boot or the cuff can use this equipment. Thus far the indication for its use appears to be in advanced arteriosclerosis of the vessels of the legs with impending or actual early gangrene. The result obtained in certain patients with such an involvement has been encouraging in that the symptomatic progress of the condi-

tion has been arrested and reversed, with improvement and healing. In this type of condition progress is slow, and we find it usually necessary to keep the patient on the bed for at least one month. Treatments of a few hours duration are not satisfactory, in our experience. We have, therefore, set a minimum in our clinic of eight hours a day. It rarely seems necessary to employ the bed for patients with thromboangiitis obliterans, since the proper use of typhoid vaccine is satisfactory in most cases.

Mecholyl Iontophoresis. Mecholyl Iontophoresis, first described by Kovacs (39), appears to have a definite place in the therapy of peripheral vascular diseases. The treatment is as follows: $\frac{1}{10}$ to $\frac{1}{2}$ per cent aqueous solution of Mecholyl is applied over the area to be treated, by means of a sheet of saturated asbestos paper. A malleable electrode is wrapped around this asbestos, making certain that no area of the skin comes in contact with the electrode. This is attached to the positive pole of a galvanic machine. A negative electrode is used on the back or elsewhere on the body. It should be a large pad, preferably ten by twelve inches and should be moistened thoroughly with water before being applied. Treatments are from twenty to thirty-five minutes duration, using from fifteen to twenty milliamperes of current.

Mecholyl is a definite and powerful parasympathetic stimulant, resulting in an increased blood flow in the local areas involved, in addition to certain general reactions which have been described in detail in various papers from our clinic. In the event of any untoward symptoms (which have been very rarely noted) an injection of atropine will bring about a prompt termination of the effects of Mecholyl. Indications for this form of therapy are as follows:

1. Post-phlebitic or varicose ulcers. This treatment is not intended to eliminate the proper treatment of varicose veins by means of injections, ligations, etc., but rather to supplement it by improving the local circulation which will help in the healing of these chronic ulcers. We have treated more than one hundred and fifty cases. Of these approximately 30 per cent have failed to respond, but many intractable ulcerated areas have been healed, including some with a continuous history for a period of from twelve to twenty-three years and which had failed to heal under a great variety of other methods and treatments.

2. Murphy (40), Montgomery (41), and others have reported some value in this form of therapy in the treatment of acute thrombo-phlebitis. We have seen a few instances in our own series in which it seemed to be helpful. It should, therefore, be kept in mind as a possibility for this type of condition.

3. Pernio. The serious ulcers of pernio (advanced chill blains) which respond to practically no other form of therapy, have been very favorably influenced by the use of Mecholyl Iontophoresis as described by McGovern and myself (42).

4. Uncomplicated Raynaud's Syndrome. Mecholyl Iontophoresis will

probably not effect the ultimate course of this syndrome, but during the cold months will decrease the frequency and severity of attacks in many patients. It tends to tide them over the severe winter months, whereas during the warm months nature provides adequate vasodilatation, and attacks do not occur with the intensity with which they do in the winter.

5. Scleroderma. While the treatment of Scleroderma, medically or surgically, has failed to produce a definite cure, Mecholyl still appears the only form of therapy which produces a definite effect in an appreciable percentage of the patients. In more than 40 per cent of our series (which was first reported by Duryee and myself (43)) a definite improvement has followed the use of Mecholyl Iontophoresis over a protracted period of time. It is often necessary for the patient to have two or three treatments a week for many months. We had in our series, for example, an Italian woman aged 54 who had been bed-ridden for seven years, unable to feed herself or care for herself in any way because of her advanced Scleroderma, involving the hands, forearms, face and various other parts of the body. Following a total of one hundred and forty treatments with Mecholyl Iontophoresis, she takes care of all her household duties, including washing and ironing and this improvement has been maintained for more than four and a half years to date. Her hands are practically normal as regards general usefulness. In certain patients, however, other portions of the body surface affected with Scleroderma have become softer and more pliable, whereas the skin of the fingers has remained most resistant to therapy.

SUMMARY

An effort has been made to evaluate the present usefulness of various physical measures in the treatment of peripheral vascular diseases. It should be pointed out that these agents represent only a portion of the whole therapeutic picture, which also includes the problems of tobacco, the local care of the lesions and of the extremities, the use of drugs, typhoid vaccine, tissue extracts, alcohol and the numerous techniques in the surgical field. Anyone purporting to treat these conditions must be thoroughly familiar with the entire field of therapy.

Physical agents are, however, important and it appears well worthwhile to review their indications and contraindications at this time. Today many of these problems are controversial. The final answers must await the accumulation of further clinical experience and experimental data.

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CALCIFICATION OF THE PERICARDIUM AND CHRONIC CARDIAC COMPRESSION

REPORT AND DISCUSSION OF FOUR CASES

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Most internists have become conscious of the existence of the syndrome of chronic cardiac compression in its full-blown form of Pick's syndrome. Beck (1) has popularized the triad of the small quiet heart, ascites, and high venous pressure as the pathognomonic criteria of this syndrome. The diagnosis of chronic constrictive pericarditis is most often employed for cases presenting this clinical picture, and the old concept of chronic adhesive pericarditis is now rarely used.

Although the outspoken syndrome is easily recognizable when the condition is kept in mind, there are still many features of chronic cardiac compression that are not generally known. For instance, the early manifestations are often overlooked. It is hoped that a report and discussion of four cases of calcification of the pericardium, which constitute only a part of the cases of chronic constrictive pericarditis that have come under my observation, will be helpful in detecting this condition in its earlier course.

PATHOLOGY AND ETIOLOGY

Thickening and scarring of the pericardium, with or without the deposition of calcium, is the essential feature of the underlying pathology of chronic cardiac compression. The precursor of this lesion is probably always an inflammation of the pericardium, rarely if ever associated with myocarditis or endocarditis. It is often impossible to determine the etiologic agent responsible for the pericarditis, and, in fact, the original inflammation of the pericardium may have passed unrecognized. The etiologic agent of rheumatic fever is probably rarely if ever the cause, since, although rheumatic pericarditis with resulting adherent pericardium and pleuropericardial adhesions is common, the thickening of the pericardium is not sufficient to compress the heart. Thus, the syndrome of chronic cardiac compression is not observed in cases of rheumatic heart disease.

Tuberculous infection of the pericardium is known to lead at times to thickening and calcification of the pericardium sufficient to seriously compress the heart. Even so, the condition of chronic compression of the heart is rarely noted among patients with clinical tuberculosis, although

pericarditis is not rare. Cases of pneumococcal and staphylococcal pericarditis undoubtedly result at times in sufficient scarring with calcification to produce cardiac compression. Influenza has also been indicted. However, a review of the literature reveals few cases in which a definitely proved etiology has been established, although numerous conclusions have been reached. For instance, of 93 cases of calcification of the pericardium collected or reported by Turner (2) there were practically none in which the etiology was clearly established. White (3) adduced a tuberculous etiology definitely in 2 of 15 cases of constrictive pericarditis and questionably in 2 others, but none of these had calcium deposits. Burwell and Blalock (4) stated that constrictive pericarditis was almost certainly tuberculous in origin in 16 of 19 cases but did not mention the incidence of calcification. It would appear best at present to keep an open mind as to the etiology of scarring of the pericardium, with or without calcification, unless it is beyond question. Only thus can accurate data be collected. A tuberculous etiology is suggested in three of the four cases to be reported, but one should not be dogmatic on that point.

Simple scarring by fibrous thickening is considerably more common than extensive calcification. The extent of the calcification varies greatly from a few plaques in a scarred pericardium to an extensive, thick casing. There is sometimes some incrustation of calcium also in the superficial portion of the myocardium.

I have not completely reviewed the literature in regard to the number of reported cases of calcification of the pericardium, but Turner (2) in 1924 collected 89 cases and added 3 of his own. Youmans (5) added 1 case in 1924 and 2 more cases in 1926. Smith and Willis (7) published their series of 15 cases in 1932. Lian, Marchal and Pautrat (8) described 2 cases in 1933. Beck and Cushing (9) noted calcification in 3 of 9 cases of cardiac compression reported in 1934. White's (3) series reviewed in 1935 contained 6 cases of constrictive pericarditis with some calcification. Turner and Moore (10) reported a case in 1937. Leaman and Vastine (11) added 1 case in 1940, and Crimm, McDonald and Cookson (12) described another in the same year. There have, therefore, been reported at least 124 cases, and the 4 now added bring the number to 128. The exact number of recorded cases is not important, but the approximate number indicates the relative rarity of the condition.

PATHOLOGICAL PHYSIOLOGY

Burwell and Blalock (4) have summarized well the circulatory alterations of chronic constrictive pericarditis. The main features are as follows, with considerable variation in some of them:

1. Increase in the venous pressure, always present, persistent but sometimes fluctuating.
2. Moderately decreased arterial pressure, usually with a small pulse pressure, and sometimes with pulsus paradoxus.

3. Small pulse.
4. Moderate tachycardia, not necessarily present.
5. Diminution of excursion of the ventricles, usually more marked on the right side.
6. Increase in total blood volume, probably common.
7. Diminished velocity of blood flow in many.
8. Decrease in the cardiac output, common.
9. Venous distention, common.
10. Engorgement of the liver, very common.
11. Edema, ascites, and pleural effusions, not always present.
12. Weakness, fairly common.
13. Cyanosis, often absent.
14. Lowered tolerance to exercise, common.
15. Electrocardiographic alterations, most commonly low voltage and inversion of T waves, sometimes auricular fibrillation, partial heart block, and right axis deviation.
16. Decrease in movability of the heart and shift of the electrical axis with change of position of the body, common.

SYMPTOMATOLOGY

There is great variation in the symptoms of chronic cardiac compression. Dyspnea on exertion is common, but it is not a frequent complaint. Enlargement of the abdomen occurs in those cases with ascites. Hepatomegaly alone rarely causes the patient to complain of abdominal discomfort or distention. Swelling of the feet or legs is not uncommon, and in rare cases edema of the face is present. Palpitation of the heart has been rather common among my patients. On physical examination the engorged cervical veins, small quiet heart, low arterial and pulse pressures, enlargement of the liver, ascites, and edema of the feet constitute a distinctive picture, but again there are many variations. Important confirmatory examinations include the venous pressure, roentgenographic examination, and electrocardiograms.

DIFFERENTIAL DIAGNOSIS

Conditions causing confusion are mitral stenosis, portal cirrhosis, tuberculous peritonitis, polyserositis, and nutritional edema.

TREATMENT

The treatment is surgical, pericardiectomy being necessary to decompress the heart. This has been well described by Churchill (13), Beck and his associates (14), Oppenheimer, Hitzig and Neuhof (15), and others. Selection of cases, determination of time of operation and number of stages of operation, extent of resection, and postoperative management require experience, judgment, and close cooperation between the surgeon and internist.

CASE REPORTS

Case 1. History. H. T., a Jewish salesman, aged 37 years, entered the Georgetown University Hospital on July 9, 1936, complaining of palpitation of the heart, weakness, swelling of the ankles, and dyspnea on exertion.

At the age of 16 years he became "run down" and entered Johns Hopkins Hospital, where he was kept in bed for a period of 4 months. He does not know what the diagnosis was at that time. Several years later he developed enlargement of the cervical lymph nodes and again went to Johns Hopkins Hospital, where the glands on one side of his neck were removed. One year later the glands were removed from the other side of his neck. At that time he had what was called tuberculous pericarditis with effusion. Five years later he developed an "eruption or abscess" in his left thigh, which was operated upon in one of the hospitals in Baltimore.

About January, 1935 he began to have attacks of palpitation. They occurred especially when he was lying in bed or after eating a heavy meal. About May, 1935, however, the attacks of palpitation became less numerous and less severe than was the case at the onset.

In March, 1935 he became "run down" and developed a continuous dull pain in his back. This pain extended from the lumbar region up to the shoulders. It completely disappeared after 2 weeks. At this time he visited his private physician who told him he had an "irregular heart." Treatment was of little benefit, and in May, 1935 he went to a hospital clinic because of weakness and palpitation. He was fully digitalized as an ambulatory patient. Two weeks later he was hospitalized at this hospital. While here his abdomen commenced to enlarge, but did not reach a great size. X-ray examinations of the chest showed evidence of fluid in the right pleural cavity. The chest was tapped and 1 pint of clear fluid was aspirated. Four days later the chest was again tapped and less than 1 pint of fluid was removed. Microscopic examination of the fluid revealed tubercle bacilli. While at this institution he developed a cough, which was associated with the expectoration of considerable sputum.

After 2 weeks' stay in this hospital he was sent to Gallinger Municipal Hospital because of tuberculosis. He remained there for 4 weeks, leaving of his own accord. While there, his sputum and pleural fluid were examined for tubercle bacilli but none could be found. During his last week there, he vomited all the food he ingested.

From July 15, 1935 to October 1, 1935 he remained at home and was treated by his private physician. He stayed in bed and became very weak.

From October 1, 1935 to February 27, 1936 he was hospitalized at the Jewish Consumptive Relief Society in Colorado. He improved greatly while there and regained his strength. After a month he was able to be up and around. The heart specialist there put him on quinidine intermittently.

In the middle of December, 1935 his right ankle began to swell; the swelling was relieved by the application of an Ace bandage. During one period, while at that institution, his abdomen became swollen, but returned to normal under quinidine therapy. On discharge he felt well.

From this institution he went to see Dr. Claude Beck in Cleveland, who said he had fibrous tissue around his heart which should be removed. He stayed there for 10 days and then returned home, where he remained until his admission into the Georgetown University Hospital. While he was home his condition became worse. In May, 1936, the attacks of palpitation recurred and he experienced muscular weakness and shooting pains around the heart. Swelling of the ankles started about June 1, 1936. It appeared first in his right ankle, then the left. He also grew weak and began to have shortness of breath, especially on exertion.

Examination. The patient was a well developed and well nourished man who did

not appear to be ill or dyspneic while at rest. The cervical veins were moderately distended. The lungs were apparently normal. The heart appeared to be slightly enlarged, and the apex beat was rather forcible; the rhythm was totally irregular and the heart rate was 80 per minute with practically no pulse deficit. There were no murmurs. The abdomen was slightly distended but without evidence of ascites. The liver was considerably enlarged, reaching 6.5 cm. below the xyphoid and 9 cm. below the costal margin in the right midclavicular line. There were varicose veins in the scrotum, a mild varicocele, and large varicose veins of the legs. Moderate edema of the ankles and legs was present.

X-ray examination of the chest showed the presence of a small amount of fluid at the right base and evidence of some pleural thickening. There were old scars at the apices. The greatest diameter of the heart was 17.5 cm., that of the thorax, 31 cm. The cardiac shadow appeared bag-shaped, and the lower part of the anterior contour of the heart, the basal portion, and the posterior half were surrounded by several

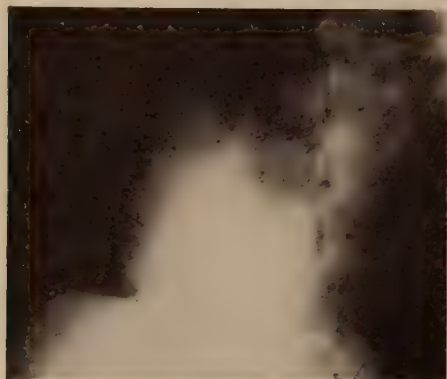


FIG. 1

FIG. 1. Case 1. Left lateral view showing diffuse calcium deposition preoperatively, March 3, 1936.



FIG. 2

FIG. 2. Case 1. Left lateral view showing partial rim of calcium three and a half years after operation, October 10, 1939.

large calcified plaques (fig. 1). The left border of the heart showed good pulsations but the right border appeared to be immovable. There was very little shift of the heart with change of position of the body.

The blood pressure was 112 systolic and 70 diastolic. The venous pressure was 260 mm. of saline solution. An electrocardiogram showed auricular fibrillation, right axis deviation, low voltage, and only slight change in axis with change in position.

There was some improvement in the symptoms and disappearance of the edema with bed rest and medical therapy.

Operation. On July 25, 1936 Dr. Beck performed a partial pericardiectomy, dissecting with great difficulty a calcified scar 2 to 3 mm. thick over the left ventricle anteriorly and laterally to the apex and along the right lateral aspect of the heart. It was impossible to dissect off the calcified plaque which was imbedded in the wall of the right ventricle. There was immediate improvement, the blood pressure rose to 135 systolic and 90 diastolic, and the venous pressure dropped to 190 mm. of saline. Before operation the cardiac output was 4.15 liters per minute with a blood volume of 7340 cc., and postoperatively the output was 3.84 liters with a volume of 6640 cc.

Postoperative course. The patient has been well and completely free of discomfort since the operation, although he is engaged in a rather strenuous occupation. The

heart has continued to fibrillate and the venous pressure has remained elevated. The liver has not been as much enlarged as before operation, but has continued to be moderately enlarged, extending downward four finger-breadths below the right costal margin. On January 22, 1941 the heart and pulse rates were 84 per minute, the blood pressure was 120 systolic and 80 diastolic, and the venous pressure had varied from time to time from 170 to 210 mm. of saline. X-ray examination shows the size of the heart to be slightly less than before operation. There is good pulsation of the left border, but very little of the right, and there is very little shift with change of position. A rim of calcium is seen in the lateral view extending over the anterior and inferior portions of the silhouette (fig. 2). Electrical stethograms do not show any abnormal vibrations. The voltage of the electrocardiogram is now normal, but otherwise there is no change (fig. 3).

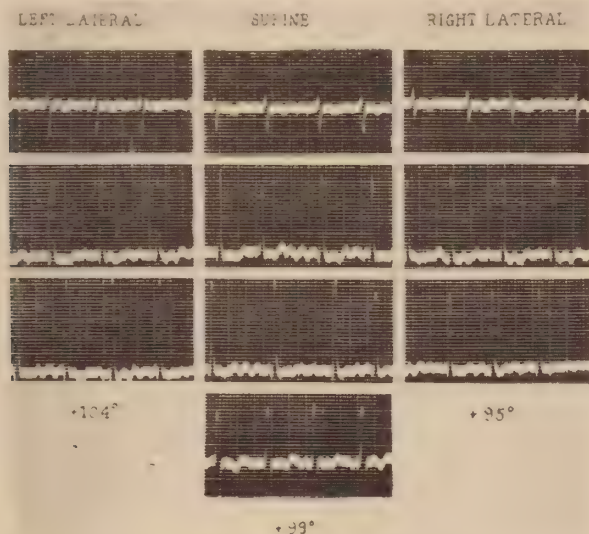


FIG. 3. Case 1. Electrocardiograms made in three positions, showing auricular fibrillation, right axis deviation, and only slight change in axis with shift of position; made years after operation (May 10, 1940); voltage now normal.

Comment. Points worth emphasizing are the absence of ascites, although the liver has been persistently enlarged and the venous pressure always high, even after the clinically successful operation; the presence of auricular fibrillation and right axis deviation, and return of the voltage to normal without any improvement in the amount of shift of the electrical axis; the relatively normal pulse rate; the lack of any manifestations of circulatory distress five years after resection of the scar over part of the left ventricle and the lateral border of the right ventricle only; and the apparent tuberculous etiology.

Case 2. History. K. K., a 39 year old carpenter of German birth and extraction, was admitted to the Georgetown University Hospital on October 5, 1939. For an indefinite period, certainly several months, he had had occasional episodes of dyspnea on exertion. About 6 months before he had had more marked dyspnea than usual, associated with some edema of the face and slight fulness of the abdomen. At that time he had remained in bed for 2 weeks and these symptoms had disappeared. He

was then able to work with little discomfort except for slight shortness of breath until about 3 weeks before admission, when he again developed increased dyspnea, some edema of the face and moderate swelling of the abdomen. Soon thereafter he had become unable to continue working. There had been occasional attacks of precordial oppression while the patient was lying down.

Previously his health had been good, but during the preceding 5 or 6 years he had felt better in hot weather and during the winter had been unable to keep his hands and feet warm. He did not recall any past illnesses except influenza in 1937. He was married and had two children. The family history was irrelevant.

A review of the functions of the various systems of the body did not reveal anything of importance.

Examination. The patient was a sturdy, well developed and well nourished man with purplish red cheeks. He weighed 180 pounds and was 66 inches tall. There was slight cyanosis of the lips, fingernails, and toenails. He was lying comfortably in bed. The cervical veins were prominent and pulsating. The retinal venules were rather more prominent than normal. The apical impulse could not be seen or felt. The area of cardiac dullness from the midsternal line to the left border in the fifth intercostal space measured 9.5 cm. (The clavicle measured 15 cm.). The heart sounds were distant and totally irregular. The rate of the heart beat was 90 per minute, whereas the pulse rate was 74 per minute. No murmurs were audible. There were some subcrepitant râles at the bases of the lungs posteriorly, but there was no evidence of pleural effusion. The liver was felt to be prominent and extended about 5 cm. below the right costal margin. The abdomen was moderately distended and there seemed to be a small amount of ascites. The left lower extremity was slightly edematous. The oral temperature was 99.2°F. During the 16 days in the hospital on the first admission the temperature remained essentially normal. The pulse rate varied from 60 to 80 per minute. The arterial blood pressure was 104 systolic and 80 diastolic in both arms. Various circulation tests performed by Dr. H. H. Hussey gave the following results:

	RIGHT ARM	LEFT ARM
Initial venous pressure in mm. of saline.....	290	295
Venous pressure during compression of liver.....	350	400
Venous pressure after opening and closing fist for 1 minute.....	340	345
Time for return of venous pressure to normal after above exercise.....	3'45"	3'45"
Arm-to-tongue circulation time (MgSO ₄).....	35"	37.6"
Arm-to-lung circulation time (ether).....	23.8"	15.4"
Lung-to-tongue time (difference between above times)....	11.2"	22.2"

A urinalysis was essentially normal. The hemoglobin was 90 per cent; the erythrocytes numbered 5,000,000 per cu. mm. of blood, and the white cells 9,800, with 76 per cent segmented leucocytes, 20 per cent lymphocytes and 4 per cent eosinophils. Blood Wassermann and Kahn reactions were negative. The sedimentation rate was 6 mm. in 1 hour. The basal metabolic rate was minus 10 per cent. Roentgenograms of the chest showed the following heart measurements: Ml, 11 cm.; Mr, 6 cm.; total; 17 cm. (internal diameter of the chest: 34 cm.). A thick layer of increased density was present around the left ventricle (fig. 4). Fluoroscopic examination of the heart in various positions showed almost normal excursion of the heart with change of position. The left ventricle seemed to pulsate almost normally, the right ventricle

hardly at all. An electrocardiogram showed auricular fibrillation (ventricular rate, 70), normal axis deviation, and inverted T waves in the three standard leads and lead 4 F. The voltage was not low. Electrocardiograms made with the patient in various positions showed practically no shift in the electrical axis in spite of the fluoroscopic evidence of movability of the heart (fig. 5). Because some physicians thought they heard an apical diastolic murmur, simultaneous electrocardiograms and stethographic records were made (by Dr. John Harper, Captain, M.C., U.S.N., at the Naval Medical School). They showed diastolic sound waves, which, however, could not be interpreted as murmurs. A tuberculin patch test performed a few days before discharge showed a marked reaction.

The fluid intake was limited to 1200 cc. daily, and the diet was salt-poor. A loss of 10 pounds in weight resulted in 2 weeks.

Course. While arrangements were being made to send the patient to Dr. Claude Beck of Cleveland for possible operation for chronic cardiac compression caused by



FIG. 4

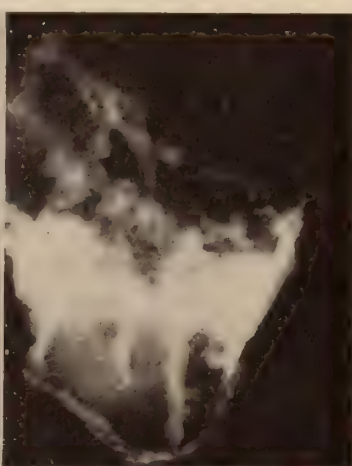


FIG. 5

FIG. 4. Case 2. Left lateral view showing thick rim of calcium around heart.

FIG. 5. Case 2. Roentgenogram of heart removed from body

calcification of the pericardium probably the result of an old tuberculous pericarditis, the patient re-entered the hospital 1 week after the first discharge therefrom because of some pain in the left hemithorax and a little blood-spitting. The temperature was 99.8°F., the heart rate 116 per minute, and the pulse rate 88 per minute. The physical examination was the same as before except for some dullness in the left lower axillary region. The weight was now 160 pounds. The liver was somewhat larger than before, but there was no evidence of ascites. A roentgenogram of the chest showed an area of complete opacity extending from the middle of the fifth intercostal space anteriorly to the base on the left side; this was thought to represent an infarct of the lung. After the first day the temperature remained normal, but within a week signs of a moderate left pleural effusion developed. At this time the sedimentation rate was 8 mm. in 1 hour. About 50 cc. of a clear, straw-colored fluid was aspirated from the left hemithorax; acid-fast organisms could not be found. The patient was discharged 11 days after the second admission and sent to the Lakeside Hospital in Cleveland, Ohio.

He remained at the Lakeside Hospital until December 10, 1939. During the

first 4 hospital days he had an elevation of temperature to 37.6°C. On the fifth day he complained of a sore throat and pain in the chest, and the temperature ranged between 39°C. and 39.8°C. for 5 days, gradually returning to a daily elevation of 37°C. to 37.8°C. Fluoroscopic examination and roentgenograms of the chest showed streaky shadows throughout both lung fields "indicating increased hyperemia." In addition, there was evidence of some fluid in the right pleural space and some elevation of the right diaphragm. Cultures of a throat swab showed alpha and beta streptococci and *Staphylococcus aureus*. Pneumococci could not be typed. The leucocyte count rose to 12,500 but promptly fell to normal. The sedimentation rate was repeatedly normal. Since it was thought the symptoms and fever might be due to active inflammation of the pericardium Dr. Beck decided to delay operation for 2 months pending subsidence of any such activity. During the period of pyrexia the patient had a moderate decrease in the urinary output, but in the last week of the hospitalization a relative diuresis occurred.

While at the Lakeside Hospital many studies were performed. Some of these were as follows. The vital capacity was found to be 50 per cent of normal. The phenol-sulfonephthalein test of renal function showed a return of 85 per cent of the dye in 2 hours. The blood non-protein nitrogen was 37.4 mg. per cent, the blood urea nitrogen 20.3 mg. per cent, and the blood uric acid 4 mg. per cent. The blood chlorides (as sodium chloride) were present in the amount of 598 mg. per 100 cc. of blood. The blood cholesterol was 164 mg. per cent. Total plasma protein measured 7.3 mg. per cent, with the albumin-globulin ratio 1:0.73. The icterus index was 13. The cerebrospinal fluid was under normal pressure and was clear, containing 3 cells; other factors were also normal. Photographic tracings of the heart sounds showed pulsus paradoxus. The blood volume was 104 cc. per kg. of body weight. The cardiac output was 35 to 36 cc. per beat. Roentgenographic demonstration of the superior vena cava by means of diodrast injected into an arm vein showed the great vein to be dilated between 2 and 3 times the normal size. The other findings and the conclusions were similar to those arrived at while the patient was at the Georgetown University Hospital.

On returning to Washington the patient remained in the Georgetown University Hospital from December 12 to December 20. No new information was obtained, but 300 cc. of slightly turbid amber fluid was aspirated from the right pleural cavity. This contained a few red blood cells and lymphocytes. Culture and smears were negative, and guinea-pig inoculation was without effect. There was no leucocytosis, and the sedimentation rate was 5 mm. in 1 hour. The temperature remained normal throughout, except that at the time of admission it was 100.4°F. There was no evidence of ascites. The weight was 165 pounds.

On a re-check on January 3, 1940 the venous pressure in the right arm was 310 mm. of saline, rising to 400 mm. with pressure on the liver. There was still no evidence of ascites, although the liver was very large and extended down to the umbilicus.

Last admission. The patient re-entered the hospital on February 11, 1940. He had been resting a great deal at home, but on February 4 he had visited a friend's house and on returning home had begun to cough and expectorate fresh frothy blood in tablespoonful amounts. The next day he fainted. Following this episode the coughing and expectoration continued, and vertigo and dyspnea followed the attacks. Examination revealed an acutely ill patient with icteric cyanosis of the face, lips, ears, fingers and toes. There was some edema of the legs. The veins of the neck were distended more than ever. Fine and coarse moist râles were heard over both lower lobes posteriorly, and there were signs of fluid in the right hemithorax. The liver was greatly enlarged, extending downward to 13 cm. below the costal margin. Ascites was definitely present. The venous pressure in the right arm was 410 mm. of saline solution and rose to more than 510 mm. with pressure on the liver. The heart

findings were unchanged, and the arterial blood pressure was 100 systolic and 90 diastolic. The temperature was 99.2°F. and the pulse rate 96 per minute. The respiratory rate was 20 per minute. On the day after admission 1600 cc. of clear, straw-colored fluid was aspirated from the right hemithorax, and following this signs of consolidation were elicited in the region of the right lower lobe which were interpreted as indicating massive infarction. The urine contained 4 plus albumin, 1 plus bile, and some hyaline casts and leucocytes. The hemogram showed 78 per cent hemoglobin, 4,300,000 red blood cells per cu. mm., and 10,700 white blood cells, with 78 per cent segmented forms and 6 per cent band forms. Roentgenograms, which had revealed evidence of fluid up to the level of the second rib anteriorly on the right side of the chest, now showed evidence of consolidation of the right lower lobe. The coughing and expectoration of blood continued, and the cyanosis became more

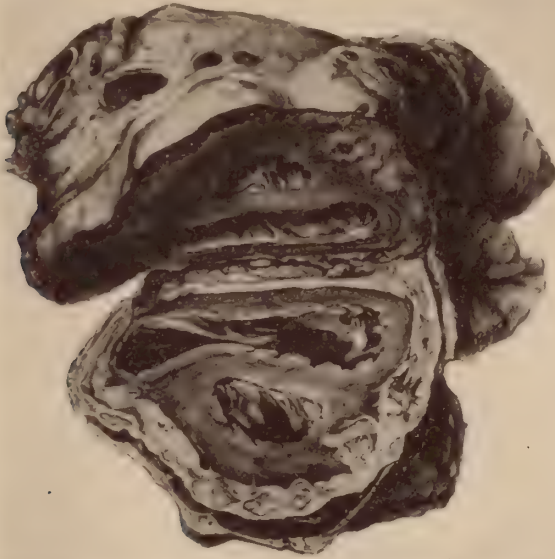


FIG. 6. Case 2. Drawing of heart bisected horizontally through ventricles and opened up, showing thick layer of calcium pericardium.

pronounced. The stools contained blood on February 15. On that day the condition became critical and oxygen was administered intranasally continuously. The patient complained of epigastric pain, and the abdomen became more distended. The temperature, which the day before had risen to 100.4°F., dropped to 97°F., and at 10 p.m. the patient died.

Necropsy findings. There was generalized chronic passive congestion. The right pleural cavity contained about 1500 cc. of bloody fluid, the left about 500 cc. of deeply yellow fluid. The peritoneal cavity contained about 2000 cc. of pale, straw-colored fluid. The right lung was atelectatic and infarcted; a large embolus filled the right pulmonary artery; the upper lobe contained small caseating, partially calcified lesions which microscopically failed to reveal tubercles. Ghon tubercles were present in the left lung, and the hilar lymph nodes were enlarged and somewhat calcified. The liver weighed about 3000 grams, was smooth, congested and mildly cirrhotic. The heart was actually not enlarged, but with the large amount of calcium throughout the pericardium appeared so (fig. 5). It felt like a rock. The

pericardium and epicardium were adherent and beneath the excessive amount of epicardial fat there was a granular deposit of calcium covering a large part of the heart, both ventricles and auricles, and attaining a thickness of more than a centimeter in many parts (fig. 6). It was not deposited uniformly, but from its site of greatest accumulation around the middle of the heart large ridges passed downward over the ventricles and around the lateral borders and apex. The coronary arteries could not be identified except at their orifices. The valves were apparently normal. A large mural thrombus was present in the right atrial appendage from which apparently a large piece had broken off. The calcium had not infiltrated the myocardium, which microscopically did not show fibrosis, but did exhibit central degeneration of the fibers with lipochrome deposition.

Comment. Outstanding features are the remarkable accumulation of calcium throughout most of the pericardium, the almost normal amount of shift of the heart with fixation of the electrical axis; auricular fibrillation with normal ventricular rate and inverted T waves in all leads, but without low voltage; the absence of ascites in spite of the very high venous pressure; the recurring pleuritis; the marked tuberculin reaction and post mortem evidence of old pulmonary tuberculosis; and the terminal pulmonary embolism with massive pulmonary infarction.

Case 3. History. J. E. W., a colored man, aged 60 years, was admitted to the Georgetown University Hospital, June 27, 1940. He said that he had been perfectly well up until the end of October, 1939, when, following the lifting of some furniture, he noted an "empty" feeling in the lower abdomen. This was followed soon after by swelling of both lower extremities. A day or so after the onset he noted burning, urgency and frequency of urination and a thick yellowish discharge at the end of urination. Chills, fever, nausea and vomiting, and pain in the epigastrium developed. Jaundice became evident on the third day, and the stools were "light in color," but the urine was not dark. He was sick about 6 weeks and was treated by a local physician but remained ambulatory. The symptoms gradually receded but were followed by persistent hiccuping. He entered Gallinger Municipal Hospital, December 14, 1940, complaining of hiccups and pain in the right lower chest.

He had had periods, for the past 4 or 5 years, mainly in the spring and fall, of indigestion characterized by epigastric distress and pain, belching, and sometimes vomiting. They would occur regardless of the type of food or whether he ate or not. Bicarbonate of soda would relieve the symptoms, but food would not.

He said that he had had a cigarette cough for the past 30 or 40 years but without expectoration. He had lost some weight since the onset of the present illness but did not know the amount. He had had several night sweats since the onset. He complained of excessive fatigability. A brother died of tuberculosis in 1905 and a sister died of the same illness in 1922. He had had no definite contact otherwise.

A review of the functional systems revealed the following data. The general health had always been good. He had used two pillows at night almost as long as he could remember and felt uncomfortable without them. He also often felt uncomfortable when lying on the left side because he could not get his breath properly. He had noted moderate dyspnea on exertion since the onset of the present illness. In 1903 his legs became swollen and remained so for a year. A doctor told him he was poisoned with coffee. Except for occasional palpitation when nervous, no other cardiovascular symptoms could be elicited.

He said he had had the "clap" many years ago. He also had acute retention in 1926 and had urethral dilatations following this.

There were no symptoms referable to the other organ systems.

In the past he had had diphtheria and measles. A herniorrhaphy was performed in 1926. No rheumatic history was obtainable. The Kahn test was negative on several occasions.

At Gallinger Municipal Hospital a diagnosis of pulmonary tuberculosis was made. However, 8 sputum examinations, one a 24-hour specimen, were negative for tubercle bacilli. X-ray examination of the chest, December 16, 1939, showed a homogeneous density overlying the lower two-thirds of the right hemithorax with a suggestion of infiltration underlying the lesion. There was evidence of infiltration and fibrosis underlying the second rib on the left. The heart and mediastinal structures were displaced to the right. Another x-ray plate of the chest, March 15, 1940, showed moderate clearing of the lesion. There was a semilunar-shaped linear shadow of increased density approximating the left border of the heart.

An x-ray study of the kidneys, ureters and bladder revealed an obstructive lesion in the lower end of the right ureter at the level of the second sacral segment. The significance was unknown.

On March 26, 1940, a bronchoscopy was performed by Dr. Harry Davies. He found obstruction of the bronchus to the right lower lobe and a moderate amount of pus. There was inflammatory swelling of the right upper lobe bronchus, probably tuberculous.

The patient was treated by the usual routine measures employed on the tuberculosis wards at the Gallinger Municipal Hospital.

On June 27, 1940, the patient was removed to the Georgetown University Hospital for further study. The history obtained was essentially the same. At no time was any fever present.

Examination. The patient was a colored man who appeared slightly younger than the stated age. He was in no discomfort. The teeth were carious and the tonsils hypertrophied. The cervical veins were engorged even while the patient was sitting upright, but they filled only from above. The trachea was displaced somewhat to the right. There was supraclavicular depression bilaterally and infraclavicular flattening. The chest was of the asthenic type. There was dullness, diminished breath sounds, and retraction of the ribs over the entire right lower chest. A few moist râles were heard at the left base.

The point of maximal impulse of the heart beat could be neither seen nor felt. Percussion indicated the left border of the heart to be in the fifth intercostal space 7.5 cm. from the mid-sternal line. (The clavicle measured 15 cm.) The sounds were moderately distant but otherwise of good quality. The second aortic sound was equal in intensity to the second pulmonic sound. There were no murmurs. The pulse rate ranged mainly from 70 to 80 per minute. The blood pressure was 110 systolic and 70 diastolic. The liver was 3 finger-breadths below the right costal margin. The surface was smooth and firm. There was no free fluid in the abdomen. The rest of the examination was not remarkable.

Course. The patient remained in the hospital for 3 weeks, during which time the temperature, pulse rate and respiratory rate were always normal.

The erythrocytes numbered 3,400,000 per cu. mm. of blood and the hemoglobin was 66 per cent. The white blood cells numbered 7,000 with a normal differential. The sedimentation rate was 24 mm. in 1 hour. Wassermann and Kahn reactions were negative. A phenolsulfonephthalein test gave a total excretion of 62 per cent of the dye given intravenously in 60 minutes. The blood non-protein nitrogen was 32 mg. per 100 cc. of blood. Urinalyses showed variable amounts of pus. The electrocardiogram revealed first degree auriculo-ventricular heart block, the PR interval being 0.29 second. The T waves were inverted in the three standard leads and in lead 4 F., with some coving of the ST segments. The voltage was not low. There was moderate shift of the electrical axis with change of decubitus (fig. 7).

The venous pressure (left arm) by the Griffith method was 245 mm., saline solution, with a rise to 270 mm. with pressure in the right upper quadrant. The arm-to-tongue time with calcium gluconate solution was 13 seconds; the arm-to-lung time with ether was 7 seconds.

X-ray examination of the chest (figs. 8 and 9) was reported as follows: The silhouette of the heart is globular, with enlargement and rounding of the right side. The size is only slightly increased. Pulsations are fair on the left side and greatly

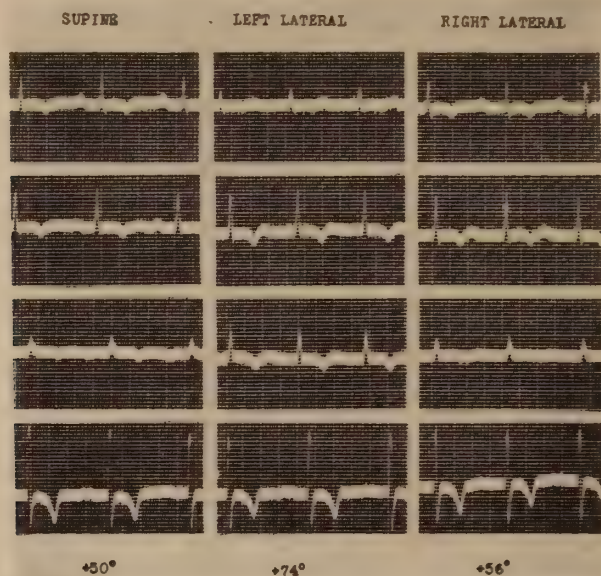


FIG. 7. Electrocardiograms made in three positions, showing PR intervals of 0.29 sec., inverted T waves, some coving of ST segments, moderate voltage, and restriction of shift of electrical axis to right.

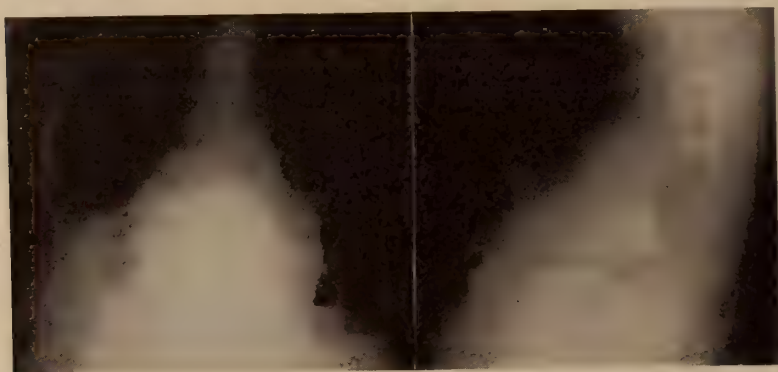


FIG. 8

FIG. 9

FIG. 8. Case 3. Anteroposterior view showing thick rim of calcium around the globular heart.

FIG. 9. Case 3. Left lateral view showing distribution of calcium over left ventricle.

restricted on the right. There is evidence of a large amount of calcium deposited in the pericardium. This is distributed largely in the form of a band which extends well up on the lateral margins above the top of the left ventricle and up into the base of the aorta on the right side. There is apparently much less calcification of the anterior

and posterior portions of the pericardium. Although there is some shift of the heart when the patient is placed in the right and left lateral positions, it is much less than normal. There is calcification throughout the right lower lobe and marked calcification of the pleura over this area. There is a small pneumothorax at the right base. Opposite the left first interspace anteriorly is an area of old tuberculous infiltration. There is scattered infiltration throughout the left lower lobe confined mostly to the inner two-thirds of the lungs. This is probably due to congestion.

Electrical stethographic records did not show any abnormal vibrations.

On April 1, 1941, a check-up showed no essential changes. The venous pressure was 250 mm. of saline. A gastro-intestinal x-ray examination revealed the presence of a duodenal ulcer. On September 23, 1941, the patient reappeared complaining of epigastric discomfort between meals and during the night and dysuria. His physical examination was unchanged. The heart rate was 68 per minute and the blood pressure was 90 systolic and 70 diastolic. The venous pressure was 200 mm. of saline solution and rose to 250 mm. with compression of the liver. The arm-to-tongue circulation time with magnesium sulfate (10 per cent solution) was 18 seconds. The use of alumina-gel in teaspoonful doses 1 hour after meals and at bed time relieved the epigastric distress.

Comment. The compression of the heart by the calcified, thickened pericardium apparently was not productive of symptoms while the patient was under observation. Ascites was not demonstrable, but the liver was somewhat enlarged. The digestive disturbance was readily explained by the duodenal ulcer and was relieved by therapy for that condition. Because of the paucity of symptoms of circulatory embarrassment, the thickness and extent of the calcification, and the advanced age of the patient, the decision was made not to attempt pericardiectomy in this case.

Points worth emphasis are the lack of ascites; the normal pulse rate; the normal circulation times; the first degree heart block, inversion of T waves, normal voltage, and presence of moderate shift of the electrical axis; and the possible tuberculous etiology.

Case 4. History. V. H. was an unmarried white woman, aged 47 years. She was first seen on March 29, 1941, complaining of having been tired and weak for 28 years, although she had been able to work as a nursemaid except for periods of rest. She had not noticed dyspnea or any sign of circulatory embarrassment. In 1931 she had been given thyroid extract and began to complain of palpitation of the heart while at work, and this had continued after the use of thyroid had been discontinued. For 6 months she had had a poor appetite with belching, water brash, nausea, occasional vomiting, and intermittent short attacks of abdominal cramps and loose stools.

As a child she had had spasmophilia and muscular pains in the legs. In 1917 she had had influenza and pneumonia, in 1921 abdominal cramps and fever, and since 1924 various gynecologic complaints and operations. She was still menstruating regularly but was having some hot flashes.

Examination. The patient was a moderately well nourished woman with very few abnormal findings. The cervical veins were not distended, and the heart seemed to pulsate well. The latter was not enlarged but presented a soft systolic precordial murmur. The heart rate was 100 per minute, and the rhythm was regular. The blood pressure was 140 systolic and 80 diastolic in the arms and 160 systolic and 100 diastolic in the legs. The lungs were apparently normal. The liver was palpable 3 cm. below the costal margin during deep inspiration. There was no ascites and no dependent edema.

X-ray examination of the chest showed the heart to be of normal size and shape, but there were numerous areas of undoubted calcification over the entire cardiac shadow. Fluoroscopic examination showed the left border of the heart pulsating

moderately well, but the right border very little. The heart moved only moderately well with change of position.

A gastrointestinal x-ray examination was negative.

Electrocardiograms showed moderately low voltage, right axis deviation, P-R interval of 0.29 second, broadened notched P waves, and depressed ST segments in the three standard leads and in lead 4 F. An injection of $\frac{1}{50}$ grain of atropine did not shorten the P-R interval. There was very moderate shift of the electrical axis with change of decubitus. Sound tracings did not show any abnormal diastolic vibrations.

The venous pressure in the right arm was 175 mm. of saline solution, with a rise to 215 mm. after compression of the liver. The arm-to-tongue time (using magnesium sulfate) was 14 seconds.

Comment. The noteworthy points are the absence of circulatory symptoms except palpitation; the absence of ascites; the evidence of cardiac compression; the slightly elevated systolic pressure; the apparently good cardiac pulsation; the first degree heart block with right axis deviation; and the absence of evidence of any definite etiologic factor.

DISCUSSION

Calcification of the pericardium of any amount probably always indicates previous severe pericarditis sufficient to result in fibrosis of that serous membrane. Therefore, whether the quantity of calcium is great or small, its presence, discovered roentgenographically, indicates some degree of cardiac compression. The manifestations of the compression are dependent upon the degree of compression and the site of greatest compression, i.e., whether in the region of one or both venae cavae, one or both auricles, or one or both ventricles. For instance, in case 1 of this series there has never been any detectable ascites, although the liver is enlarged and the venous pressure is quite high; furthermore, removal of the calcium over the ventricles resulted in clinical cure in spite of the persistence of enlargement of the liver, high venous pressure, auricular fibrillation, etc. This result indicates that although there is definite inflow obstruction, compression of the ventricles is also an important factor, preventing them from both filling and emptying properly.

None of the four patients had demonstrable ascites except in case 3, in which it was mild and transient. It is probable that not only is it obstruction of venous blood to the heart but even more particularly obstruction of the inferior vena cava and hepatic veins that determines the presence and degree of ascites. These four cases demonstrate that ascites is not a necessary sign of chronic cardiac compression and, therefore, cannot be depended upon in establishing the diagnosis. In fact, it is probably more often absent than present, certainly in my experience.

The symptoms are quite variable. There may be few referable to the circulatory system. The most common are dyspnea on exertion, palpitation of the heart on exertion, and enlargement of the liver, but even one or more of these may be lacking. One may only speculate on the relative importance of the persistence of compression over a long period of time and progressive contraction of the scar in bringing about the advanced symp-

toms of circulatory distress. One may assume that long-standing compression of the heart impairs the nutrition and tone of the myocardium which augment the degree of circulatory embarrassment.

The venous pressure is elevated in both the upper and lower extremities, indicating central venous obstruction. Pressure of the right upper quadrant of the abdomen causes a considerable increase in the venous pressure as in congestive heart failure.

Circulation time tests give very different results in different cases. They may be within normal limits or prolonged with the same increase of venous pressure. The explanation of this phenomenon is not clear. Perhaps the opening up of the peripheral blood vessels and increase in blood volume are important in this connection. It appears rather certain, however, that the degree of clinical circulatory distress runs parallel with the increase in circulation time much more than with the height of the venous pressure.

Often there is moderate tachycardia, but the pulse rate may be normal or even slow.

The arterial pressure is usually moderately low. The pulse pressure is variable; it may be increased or decreased, more often the latter.

Roentgenography is naturally necessary to establish the diagnosis of calcification of the pericardium. As in cases of noncalcific pericardial scars the heart shape may be deformed; it is perhaps more often globular in cases of calcification. Enlargement, if present, is usually moderate and explicable by the thickness of the pericardium itself. The left border of the heart often seems to pulsate well, whereas the right side usually appears to pulsate very little. The degree of movability varies greatly from no decrease to practical fixation.

Auricular fibrillation existed in two of the four cases, considerably prolonged P-R interval in two, right axis deviation in two (one with auricular fibrillation), inverted T waves in two, depression of the ST segments in two, low voltage in two, and restriction of shift of the electrical axis in three. There were no abnormal sound waves in diastole. The protodiastolic vibration of Lian et al. (8) did not occur in these four cases.

SUMMARY AND CONCLUSIONS

Four cases of calcification of the pericardium have been reported, all showing definite evidence of chronic cardiac compression. It is a relatively rare lesion but is probably always associated with sufficient fibrosis and rigidity of the pericardium to handicap the heart in its function. Ascites is not the constant feature usually thought, and symptoms of circulatory embarrassment may be slight. Partial heart block occurred in two of the cases, auricular fibrillation in two, and right axis deviation in two. Operation is naturally more difficult than in the cases of cardiac compression without calcification. A probable tuberculous etiology existed in one case and a possible tuberculous etiology in two others. In the fourth, no etiologic agent was suggested.

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OLD AGE IN ANCIENT EGYPT
A CONTRIBUTION TO THE HISTORY OF GERIATRICS

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"Blessed is the man of science who enjoys the great companionship of the ancients; they are flesh of his flesh, sharers of his successes and errors, of his joys and his deceptions."

Sudhoff—Essays.

Primitive man is believed to have first appeared in the Pleistocene or Glacial Period, generally considered to have covered about one million years. Since many geologists now place the origin of *Homo Sapiens* in the period preceding the Pleistocene, the Miocene, the age of prehistoric man is further increased. These figures, although only approximate, contrast strikingly with the very brief time which has elapsed since the dawn of "antiquity," inaugurated by the Egyptians with the discovery of the use of metals and the development of the art of writing. According to Breasted (1), the transition from prehistory to the historic period in Egypt occupied the thousand years from 4000 B.C. to 3000 B.C. Relatively speaking, the Egyptian civilization is modern, and the progress of the past 5000 years absolutely breath-taking, however little the mind of man may have been altered in its essential nature. Hooton (2) writes that "the period of human civilization is as inconsiderable in man's cultural history as is post-glacial time in the age of the earth".

At the opening of the Age of the Pyramids in the year 3000 B.C. we find already a highly developed Egyptian civilization, characterized by intricate social organization, extensive industrial and agricultural activity, and a religious system notable for its beliefs not only in life after death but also in "right living, in kindness to others, and that a good life here was the only thing that could bring happiness in the next world" (1). This period is outstanding in giving us Imhotep, the first physician known by name, whose activities covered with distinction the fields of medicine, priestly wisdom, magic and architecture. His reputation increased steadily after his death until he became deified and later was identified by the Greeks with their own Asklepios.

The development of Egyptian medicine from the rites of the priest-magicians has been traced by Dawson (3). He has pointed out in detail

how these practices were copied by Greek and Roman writers, were transcribed in the leech books of the sixteenth century (4), and reappear from time to time in the folk medicine of our own day. The art of the magician consisted in the utterance of spells and incantations, accompanied by manipulation of figures, amulets or a variety of natural substances. These procedures have been differentiated by Gardiner (5) into the "oral rite" and the "manual rite." In the medical papyri preserved to us from these remote times we find abundant illustrations of these two rites.

"The prescriptions in the medical papyri are but elaborations of the manual rite of the magician, and it is for this reason that the papyri are interspersed with magical spells that constitute the oral rites belonging to each group of prescriptions that follows and that are recited by the magician in order to make the doses effective. Some of these remedies contain drugs that are really beneficial and appropriate, and such prescriptions, actually accomplishing their purpose, would tend to survive their more fantastic fellows. By such means more and more reliance came to be placed on the drugs themselves and less upon the magicians' spells, and the persons who would be most in request in cases of sickness would be those who were skilled in knowledge and preparation of drugs. Such men were no longer magicians, but physicians." (3)

In the famous medical document known as the Edwin Smith Surgical Papyrus (1600 B.C.), and recently published by Breasted (6) in a brilliant translation, with a beautiful reproduction of the original text, we find a remarkable description of surgical conditions of the head. These clinical records of actual cases are comparable for detail and accurate description to those of Hippocrates. Our present interest centers on the incantations and recipes which are found on the back of the papyrus in the hand of the same scribe. Among these is one entitled, "The Book for Transforming an Old Man into a Youth of Twenty". This may be divided into two parts, the first containing directions for compounding the ointment, the second, the directions for its use. These read as follows:

"Anoint a man therewith. It is a remover of wrinkles from the head. When the flesh is smeared therewith it becomes a beautifier of the skin, a remover of blemishes, of all disfigurements, of all signs of age, of all weaknesses which are in the flesh. Found effective myriads of times."

In this recipe of an Egyptian priest for rejuvenation we find the earliest written history of medicine in the aged.

The medical papyri are written in the Egyptian script known as hieratic, which must be transcribed into hieroglyphic before an English translation is possible. Study of Breasted's hieroglyphic text of the Smith Papyrus brought to this writer's attention an interesting feature of the hieroglyph meaning "old" or "to grow old". It is a clear representation of a bent

human figure resting on a staff (figs. 1 and 2). This ideograph delineates old age as typified by muscular and bony weakness, and may be considered the earliest artistic representation of senile debility. The symbol is first found in inscriptions of the period 2700 to 2800 B.C. It is to be compared with the hieroglyph for youth which consists of a sitting child with its finger in its mouth.

The Papyrus Ebers (c.1550 B.C.) (7, 8) is made up of a great collection of prescriptions for various ailments, some observations on symptomatology and diagnosis, and an unusually perspicacious description of the function of the heart and great vessels. Among the diseases and symptoms, which are

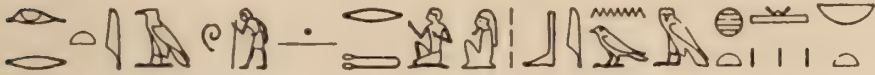


FIG. 1. Hieroglyphic sentence from the Papyrus Prisse (c. 1580 B.C.) containing the Precepts of Ptah-hotep: "To be an old man is evil for people in every respect". (Quoted by Breasted, *The Edwin Smith Surgical Papyrus*, p. 493). Note the seventh symbol from the left, which is enlarged in Fig. 2.

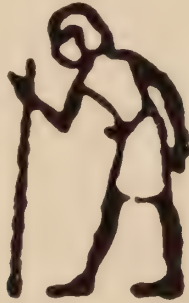


FIG. 2. This bent human figure resting on a staff is the hieroglyphic ideograph indicating "old age" or "to grow old", and used as a determinative in phrases involving the concept of old age. First noted in inscriptions of 2700 to 2800 B.C.

associated with old age, treatment is prescribed for the following: polyuria, accumulation and obstruction of urine, cystitis, cardiac pain, weakness, and palpitation, tumors, both innocent and malignant, deafness, and eye diseases. The identification of many Egyptian medical terms is often beyond the ability of the translator, who is forced to reproduce in his text the consonants representing the original word. The drugs and medicaments are of infinite variety, being derived from the animal, vegetable and mineral worlds. Many remedies are offered for constipation, grey hair, baldness, wrinkles, as well as the more serious diseases of old age.

In the section of definitions of medical terms we find an explanation of the manifestations of age. "As to debility through senile decay, it is (due to the fact) that purulency is on his heart" (8). Although the importance

of the heart for life seems to have been sensed, the Egyptians can in no way be said to have foreshadowed Harvey's great discovery (9). In the section devoted to ocular diseases we find a recipe for cataract which serves to exemplify many of the features characteristic of Egyptian medicine.

Another to expel water suffusion in the eyes:

"Come, malachite! Come, malachite!

Come, thou green one, come discharge from Horus' eye,

Come secretion from Atum's eye, Come fluid that has come out of Osiris!

Come to him and expel for him water, matter, blood, dim sight, BȝDȝ, blindness, blear-eyedness, afflictions caused by a god, by a dead man or woman, all kinds of purulency, all evil things that are in these eyes."

Is recited over malachite, pounded with honey NTHPRȝI, with them is pounded rush nut, applied to the eye. Really excellent (8).

This typical incantation embodies the oral and manual rites, the reference to the healing power of the gods and to the possible etiology in the disfavor of the gods or of a dead person, and the use of a copper compound in the eye, a practice prevailing at the present time.

All studies of Egyptian thought indicate that not only was old age held in highest respect but that the attainment of 110 years was the ultimate in achievement for an Egyptian. The inscription on a statue of Amenophis, the son of Hapu, who rivalled Imhotep as a healer, bears the inscription: "I have attained the age of 80 years, may I live to be 110." In the Papyrus Prisse (c. 1580 B.C.) we find the precepts of Ptah-hotep, a vizier in the reign of Pharaoh Assa of the Fifth Dynasty, who endeavored in his book to pass on to his children the knowledge he had accumulated during a long life. Dawson (10) calls it the oldest Wisdom Book in the world. The final words of the papyrus are: "I have gathered 110 years of life, for the King granted more favors than my ancestors, because I acted with truth and justice for the King until my old age."

Egyptian medicine flourished among a people in whom family life was highly developed. The children showed the greatest respect for their parents, and every son was required to maintain the tomb of his father. High value was placed upon the affection of one's parents and family. The inscription is found commonly in tombs: "I was one beloved of his father, praised by his mother, whom his sisters and brothers loved" (11). Thus we find here in the ancient land of Kemi not only the beginning of the medical study and treatment of the old, but also the earliest indication of the mores that were to characterize the religion of the ancient Hebrews and find lasting preservation in the Old Testament.

The writer is indebted to Mr. Ambrose Lansing, Curator of Egyptian Art, Metropolitan Museum of Art, New York, for the kindly encouragement and helpful advice of a true scholar.

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ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

A Human Cortical Area Producing Repetitive Phenomena When Stimulated. R. M. BRICKNER. J. Neurophysiol., 3: 128-130, March 1940.

During the electrical exploration of a human cortex, an area was found which when stimulated produced perseveration of speech. The area (area X) lay on the mesial side of the left hemisphere, in area 6, probably just above the junction of that area with the posterior part of area 32.

The patient, under local anesthesia, said the alphabet. At each application of the stimulus, and throughout the period of stimulation, the letter the patient was saying was repeated over and over again. The perseveration ceased instantly when the stimulus was stopped.

Area X is far from any known part of the speech zone. It influenced the function of distant neurons, and in such a way that these neurons were thrown into action again and again, as though the impulse were imprisoned in a given cell group, able to activate that group only, but unable to pass to another.

Treatment of Pruritus Ani by Tattooing with Mercury Sulfide. R. TURELL, A. M. BUDA, AND A. W. M. MARINO. Arch. Dermatol. & Syph. 41: 521, March 1940.

The authors have treated 22 patients with intractable pruritus ani by tattooing the anal and perianal regions with mercury sulfide. The results obtained have been so satisfactory as to justify a continuation of this form of therapy. Two private patients were followed for more than nine months and the clinic patients for seven months. A prolonged follow-up period will be necessary for the final evaluation of this therapeutic procedure. There was a recurrence in one patient, which took place fourteen weeks after tattooing and disappeared spontaneously. The *modus operandi* of this form of treatment is unknown. The mercury may have either an antiseptic action or a chemical effect on the cutaneous nerve supply. To determine whether the drug was necessary or not, four patients were treated with the tattoo machine without the use of mercury sulfide. Freedom from pruritus was obtained for less than three weeks. In all cases, the recurrent pruritus disappeared permanently after the tattooing was done with mercury sulfide. The authors feel that in the occasional case the psychic element is as important as the physical and chemical aspects.

Recklinghausen's Disease. Its Elusive Manifestations and Internal Relations. O.

L. LEVIN AND H. T. BEHRMAN. Arch. Dermat. & Syph. 41: 480, March 1940.

The authors have reviewed the literature and presented their views on the pathogenesis of this syndrome. They believe that the disease is hereditarily transmitted as a dominant genetic characteristic. The origin of the tumors is mesodermal, from

the connective tissue sheath of nerves (perineurium). The use of a more detailed cutaneous classification is suggested. The presence of pigmentation without tumor formation is of frequent occurrence and is a definite phase of the disease. Besides the cutaneous features, there are frequently associated motor, sensory, skeletal and mental disturbances. The great majority of patients would show definite signs of glandular aberration if they were carefully examined for these abnormalities. A syndrome with so great a multiplicity of symptoms should not be designated by a term such as neurofibromatosis which describes but one of its phases. At the present level of knowledge the most comprehensive title is still Recklinghausen's disease.

The Prognosis of Nephritis and Nephrosis in Childhood. H. SCHWARZ, J. L. KOHN AND S. B. WEINER. New York State J. M. 40: 6, March 1940.

A clinical study was made of 388 children with nephritis covering a period of 25 years. Over 60 per cent of these cases were followed for an average of 5 years. These patients fell into four clinical groups: 1) Acute nephritis; 2) chronic nephritis, clinically non-progressive type; 3) chronic nephritis, clinically progressive type; 4) lipid nephrosis. The immediate mortality in the acute nephritis was 5 per cent. Apparently 85 per cent recovered fully and the remaining 10 per cent developed chronic nephritis either progressive or non-progressive. Of the patients admitted with a diagnosis of chronic nephritis over 50 per cent died within a year. Only 8 per cent have lived longer than 5 years. In our series of lipid nephrosis mortality was 50 per cent in the first year. Twenty-five per cent of the patients apparently recovered. This has been confirmed by a long follow-up. We feel that lipid nephrosis is distinct from chronic nephritis.

The Intestinal Phase in Urologic Disease, III. The Role of the Colon in Urolithiasis. R. TURELL. J. Urol. 43: 476 March 1940.

The literature dealing with the relation of infection to urolithiasis is reviewed. The author believes that preexisting uroinfection caused by the organisms of the colon bacillus group and inflammatory and suppurative lesions and dysfunction of the anorectocolonic tube are important causative factors in the genesis of urolithiasis in certain cases. The eradication of the foregoing lesions and the correction of dysfunction are an important part of the therapeutic program for the elimination and prevention of urolithiasis with infection caused by organisms of the colon bacillus group.

Recovery in Amyotrophic Lateral Sclerosis (Treated with Tocopherols, Vitamin E). Preliminary Report. I. S. WECHSLER. J. A. M. A. 114: 948-950, March 1940.

The author reports two cases of amyotrophic lateral sclerosis which responded to treatment with vitamin E. The first patient was a man, 52 years of age, who had weakness of one hand with fibrillations, atrophy and increased reflexes for three months before coming under treatment. Following the administration of vitamin E, the weakness disappeared and the atrophy receded. The second patient was a woman, 36 years of age, who had a very advanced form of the disease including bulbar signs. Following the administration of vitamin E, the fibrillations and the atrophy of the tongue disappeared and her general strength increased so that from a bedridden patient she could walk about the room with assistance. Without making any claims that the absence of vitamin E is the cause of amyotrophic lateral sclerosis or the administration is its cure, the author merely records the facts and suggests further clinical experimentation.

Subacute Yellow Atrophy of the Liver. With Unusual Abdominal Venous Bruit. H. HERMAN. J. Pediat. 16: 507, April 1940.

A brief discussion of the relationship between acute and subacute yellow atrophy, catarrhal jaundice, cirrhosis, hepatitis and hepatosis served to introduce a case of subacute yellow atrophy of the liver in a Jewish girl of 10 years. The condition was entirely silent until the terminal illness which lasted four weeks. The laboratory examination suggested severe liver damage before the clinical picture did. The etiological factors remain undetermined after autopsy, the findings of which were reported. The liver was half the normal size, and presented a striking picture of yellow atrophy of long standing with nodular areas of regeneration. The presence of a venous bruit, with a study of the accompanying regional pathology was of particular interest.

Treatment of Ocular Syphilis. O. L. LEVIN AND H. T. BEHRMAN. Arch. Ophth. 23: 693, April 1940.

Experience and observations in the treatment of ocular syphilis are described. The accepted modern forms of therapy are indicated and the dosages and drugs are discussed in detail. Proper techniques, including suggestions for the avoidance of Herheimer reactions, are carefully discussed. The Swift-Ellis method of intra-spinal therapy is advocated in resistant ocular syphilis associated with neurosyphilis. Other forms of supplemental treatment, such as hyperpyrexia, and their value in the different phases of syphilis of the eye are commented upon. The recent trends in the therapy of ocular syphilis offer a much more hopeful prognosis than is generally believed.

The Value of the Sedimentation Time in Suppurations of the Anorectal Tissues. R. TURELL AND A. W. M. MARINO. Am. J. Clin. Path. 10: 300, April 1940.

The authors have employed the phenomenon of sedimentation of erythrocytes in the diagnosis of obscure suppurations in the anorectal tissues. Their studies showed accelerated rates of sedimentation of the red blood cells in cases of suppuration in the anorectal tissues, and normal rates in cases of nonsuppurative lesions. In one case of fistula in ano sedimentation rates were recorded from the early onset of infection of a crypt of Morgagni to the time of complete postoperative healing. Preoperatively, as the lesion was progressing, the sinking of the erythrocytes was correspondingly rapid until a fistulous tract with drainage through the primary and secondary openings was established. Postoperatively, there was a gradual decrease in the rapidity of the sedimentation of the red blood cells as healing progressed. This test demonstrated the progress of the suppurative process more accurately than did the clinical examination. The fluctuation of the rate of the sinking of the erythrocytes closely paralleled the development of this lesion in its relation to drainage.

The employment of this test prior to injection of oil-soluble anesthetics in the ambulatory treatment of fissures is of value. It is also useful in determining the character of postinjection reactions. The place of this test in the evaluation of the anorectal symptoms in the psychoneurotic patient whose complaints are out of proportion to the existing lesions was also discussed.

The study of the sedimentation time of the erythrocytes is valuable in the differential diagnosis of acute anal pain.

Transfusion of Blood from Artificially Immunized Donor in the Treatment of Chronic Bacillary Dysentery. R. TURELL. J. Lab. & Clin. Med. 25: 706, April 1940.

The author recorded his observations with transfusion of 300 cc. of blood obtained from a donor who was artificially immunized with a vaccine prepared from an atypical Flexner paradysenteriae organism isolated from the ulcers of the recipient's colon. The beneficial effect upon the diarrhea was prompt and clear cut. On the third day following immunotransfusion there was a drop in the number of leucocytes in

the blood from 20,600 to 7,250, while the effect on the hemoglobin and the number of the erythrocytes was negligible.

The practical results obtained in this patient and the theoretical basis of this method appears to justify an extensive trial of this type of immunotransfusion in order to determine its proper place in the therapy of chronic bacillary dysentery.

Carcinoma of the Nasopharynx with Extension to the Petrous Pyramid. J. DRUSS. *Laryngoscope* 50: 359, April 1940.

Carcinoma of the nasopharynx because of its relative inaccessibility and very high mortality rate is one of the most dread conditions with which the otolaryngologist is confronted. Because of the insidious nature of its growth and sparsity of early manifestations it is frequently undiagnosed until late in the course of the disease. Not infrequently physical signs and symptoms, chiefly pain, tinnitus and impairment of hearing are related to the ear. A case of carcinoma of the nasopharynx with extension to the petrous pyramid is presented. The importance of early and careful examination of the nasopharynx in all instances of unexplained hemicranial pain, aural symptoms or cervical adenopathy is emphasized.

Treatment of Rickets and Tetany by Parenteral Administration of One Massive Dose of Vitamin D. H. VOLLMER. *J. Pediat.* 16: 419, April 1940.

The harmlessness of one single dose of 600,000 units of vitamin D is shown theoretically and is practically demonstrated by its administration to 158 children in whom no toxic manifestations occurred.

The parenteral administration of one massive vitamin D dose is recommended for certain clinical purposes. The absorption of parenteral vitamin D depots can be accelerated by using a mixture of oil and ether instead of oil alone as a solvent. The superiority of an oil-ether mixture in this respect is demonstrated by animal experiment.

Rickets and tetany respond to this form of parenteral vitamin D shock therapy as promptly as to the oral administration of equal doses of vitamin D. Serum calcium and phosphorus become normal usually after three to seven days. Roentgenographic evidence of calcification shows within one week, and recalcification is usually complete thirty days after the beginning of the treatment. Tetanic convulsions cease within 24 hours after the parenteral administration of one massive dose of vitamin D. Prevention of rickets in premature infants with parenteral administration of single massive doses of vitamin D has also been carried out successfully.

The Medical Management of Hyperthyroidism. H. T. HYMAN. *Bull. New York Acad. Med.* 16: 265, May 1940.

The clinical management of hyperthyroidism requires a complete understanding of the physiology of the thyroid gland and the involuntary nervous system. The obvious conception of hyperthyroidism alone is not sufficient to explain the syndrome as it appears in the individual patient.

Present knowledge of clinical hyperthyroidism may be summarized by the statement that it is a complicated syndrome consisting of neurogenic, metabolic and glandular components. Broadly stated, there is present: 1) diminished storage of iodine in the gland, giving rise to hyperplasia; 2) sympathomimetic symptoms and 3) a general increase in catabolism.

The diagnosis of hyperthyroidism is often too inclusive, embracing individuals with neuroses and no metabolic disturbance; those with a simple goiter and others with autonomic imbalance.

Again, the diagnosis may be overlooked particularly in thyro-cardiac invalids.

Though the spontaneous course of hyperthyroidism is toward remission or recovery, the restitution of the patient calls for specific therapy with iodine, followed by a subtotal thyroidectomy. The latter should be considered an incident in the therapeutic program. Both pre-operative and postoperative management require the services of the practitioner or internist who may the better deal with the individual components of this complicated clinical problem.

An Experimental Study of the Chemical Content of Sweat. O. L. LEVIN, S. SILVERS AND H. T. BEHRMAN. *Urol. & Cut. Rev.* 44: 307, May 1940.

The data presented in this article indicates that there is a great variation in the total nitrogen of sweat. In addition, changes in the urea nitrogen, sugar concentration and the chloride content of sweat were observed in normal individuals and in patients with various skin diseases. The sweat concentration in pruritus and eczema showed no diminution in chloride content. The results of these experiments failed to show any real difference in the sugar concentration of the sweat in cases of acne vulgaris or of follicular and pustular dermatoses. The sweating response was delayed in eczema, seborrheic dermatitis, ichthyosis and parapsoriasis. All of the variations noted in male patients were comparable to those observed in female patients, although the latter formed a much smaller group.

Present Day Conception and Treatment of Acne Vulgaris. O. L. LEVIN AND H. T. BEHRMAN. *Med. World.* 58: 310, May 1940.

This paper discusses the pathogenesis of acne vulgaris. Etiological factors, aggravating agents and clinical types are thoroughly reviewed. General and local measures of therapy are described in detail. The authors state that the modern treatment of acne has completely changed the former depressing outlook. General measures should never be neglected and local therapy should resolve itself into treatment of the pathological state present. The final cosmetic result is of paramount importance and may be attained by management of each case as an individual problem.

Arteriosclerosis of the Coronary Arteries and the Mechanism of their Occlusion. H. HORN, AND L. E. FINKELSTEIN. *Am. Heart J.* 19: 655, June 1940.

The results of a study of one hundred unselected autopsy cases of recent occlusion of the coronary arteries and a review of the literature are presented. Contrary to common belief, the individual artery most frequently the seat of acute occlusion was the right coronary artery. Simultaneous, multiple occlusions of the coronary arteries were frequent. Vascularization of the intima of the coronary arteries was found only in the presence of arteriosclerosis. Vascularization is regarded unequivocally as a sequel of the degenerative changes in the intima. Once established, however, the capillary network becomes an important factor in the advance of the arteriosclerotic process. Intramural hemorrhage was observed frequently, and was always found to be associated with vascularization, and plaque degeneration.

Coronary artery occlusion may be produced either by intramural hemorrhage (62.5 per cent) or by the formation of a thrombus on an arteriosclerotic plaque (37.5 per cent). Intramural hemorrhage was found to lead to coronary artery occlusion either by inducing acute degenerative and reactive responses in the plaque overlying the hemorrhage, by obstructing the artery mechanically, or by actually producing dissolution and rupture of the intimal layer. The extent and variety of change are dependent upon the relationship between the vascularity of the plaque and the degree of degeneration therein. Coronary artery occlusion produced by deposition of a thrombus on a plaque is usually secondary to an edematous, acute, reactive or

degenerative change in the subendothelial tissue. Evidence that coronary artery occlusion may be a slow progressive process is found in the coexistence of recent and organizing changes within a plaque or its thrombus.

Judging from this morphologic analysis, coronary artery occlusion is believed to be a fortuitous incident in arteriosclerosis. The direct, immediate, precipitating factors underlying recent occlusive changes could not be ascertained in this survey.

Estrogenic Effects upon Tubal Contractility and the Vaginal Secretion in the Menopause.

P. BERNSTEIN AND M. FERESTEN. *Endocrinology* 26: 946, June 1940.

Tubal contractions of 24 menopause women were studied before and after estrogenic therapy by uterotubal insufflation. The vaginal secretion was also studied in 19 cases. In at least 62.5 per cent of the climacteric patients, tubal function was lower than that found by Rubin in normally menstruating women. In 13 of 19 menopause patients (68.4 per cent), all vaginal smears showed follicular characteristics (high estrogen levels). In the 6 remaining patients (31.6 per cent) we found the atrophic pattern (low estrogen levels). There was no constant correlation between the type of vaginal smear and tubal function. Estrogenic therapy increased uterotubal tone and tubal contractility in over three-fourths of the patients. In all 6 cases showing the atrophic vaginal pattern, the vaginal smear picture was advanced after estrogenic therapy to the follicular phase.

Neoplasms Involving the Middle Ear. H. ROSENWASSER. *Arch. Otolaryng.* 32: 38, July 1940.

The futility of any form of treatment for advanced malignant growth affecting the middle ear is shown by Case 1, a squamous cell carcinoma in which the tumor at operation had already extended into the temporal lobe and by Case 2, in which the tumor, an adenocarcinoma, had very extensively eroded the tempora mandibular joint and zygoma. Case 3, a fibrosarcoma was not operated upon, but was apparently well, free of symptoms, for three years following intensive external irradiation. In Case 4 there was no improvement in the facial paralysis after radical mastoidectomy followed by intensive radiation therapy.

Growths situated deep in the external auditory canal should be regarded as potentially malignant regardless of whether they are associated with facial paralysis, pain, or bloody discharge. A single negative biopsy does not remove the possibility of malignancy. Patients with long standing chronic middle ear suppuration with polypi may develop a superimposed neoplasm at any time during the course of the infection, and the onset of pain, bloody discharge, or peripheral facial paralysis may be the first manifestation.

The consensus is that radical electrosurgical removal combined with intensive external irradiation is the method of choice in the treatment of neoplasms involving the middle ear.

Tattooing (Puncturation) with Mercury Sulfide and Other Chemicals for the Treatment of Pruritus Ani and Perinei: Further Investigations. R. TURELL. *J. Invest. Dermat.* 3: 289, August 1940.

At present the author tattoos not only patients with intractable pruritus ani of long standing who failed to respond to established therapeutic measures, but also those patients who have pruritus ani that is refractory to treatment regardless of the duration of the itching, as well as the few so-called psychoneurotic patients with cutaneous perianal changes consistent with pruritus ani. The results show that this form of treatment is also effective in patients in whom there was a spread of the pruritus from the posterior to the anterior perianal areas involving the perineum and the posterior portion of the vulva. Tattooing with mercury sulfide is apparently

of little value in pruritus vulvae and perinei of undetermined origin or with superimposed dermatitis. This form of therapy is under no circumstances carried out in the presence of inflammatory and infectious disease of the preformed anal ducts, anal glands, and the crypts of Morgagni. All anal lesions are always extirpated prior to tattooing. Operation and tattooing are never done during one procedure because the primary operation may control the itching in many cases and because in the presence of open wounds the mercury sulfide may get into the subcutaneous tissues and form mercury albuminate which is toxic because it is gradually absorbed. In the present series of thirty-seven there were three cases of recurrence of pruritus ani following tattooing but in no instance was the recurrent anal pruritus as intense as the original itching. Studies now in progress appear to show that a pharmacodynamic degenerative effect on the cutaneous terminal nerve supply is produced by tattooing with mercury sulfide which alters the capacity of the terminal nerve network to respond to adequate stimuli. The alteration of the sensory cutaneous modalities is within limits proportional to the amount of the intracutaneous deposit of mercury sulfide.

Rheumatic Pericarditis with Effusion Treated with Salicylates. E. P. BOAS AND M. ELLENBERG. J. A. M. A., 115: 345, August 1940.

Salicylates, in doses up to 15 grams a day, were used in treating twelve cases of rheumatic carditis associated with pericardial effusion. These uniformly resulted in a rapid reduction in the pulse rate and a resorption of the precordial exudate with consequent relief of dyspnea and toxemia. Objective evidences of improvement were found in the sharp decreases of the elevated venous pressure and in the diminution of the cardiac shadow. It was not necessary to perform pericardial paracentesis even though, in some instances, it seemed urgently indicated.

The action of the drug in these cases is analogous to its action in rheumatic arthritis with effusion, i.e. there are a rapid absorption of exudate and decrease in fever. The drug exerts no effect on the rheumatic infection, or rheumatic endocarditis and myocarditis.

Vaccinia of the Eyes. J. LAVAL. Arch. Ophthal. 24: 367, August 1940.

Two cases are reported of vaccinia of the eyes occurring in children who had been vaccinated on the left upper arm and in both of whom the ocular involvement was on the right side. In both cases the conjunctivae and lid margins were involved but the corneae were unaffected. Rapid recovery occurred in both cases with local treatment plus the administration of sulfanilamide by mouth. It is suggested that possibly the sulfanilamide was of some help but more cases would have to be treated and observed before any definite conclusions could be drawn. A resumé of the literature is included and the theories as to the mode of infection and the rôle of immunity in these cases is discussed.

Bullous Schick Reactions: Their Occurrence During Acute Infectious Diseases.

A. E. FISCHER, B. RUBIN AND C. K. GREENWALD. Am. J. Dis. Child. 60: 304, August, 1940.

Positive Schick reactions which develop blebs or bullae have been observed to occur when the test is performed during the acute stage of many of the infectious diseases, i.e. pneumonia, measles, scarlet fever, poliomyelitis, etc. The reaction seems to be associated with the presence in the body of an acute infectious agent, for the reaction has not been observed thus far in normal healthy children. Furthermore when children who develop bullous positive Schick reactions are re-tested following their acute illness a normal positive or even a negative reaction may be found. Titration of the serum for diphtheria antitoxin show that some of these patients have

only a small amount of circulating antitoxin. Surprisingly, however, although the test may change within a week or two, the amount of circulating antitoxin is not appreciably altered. Children showing the bullous type of reaction should not be considered susceptible to diphtheria unless they show a normal positive Schick reaction some time after recovery from the acute illness.

Tattooing (Puncturation) with Mercury Sulfide for the Treatment of Intractable Pruritus Caused by Leukoplakia-Kraurosis Vulvae. R. TURELL. *Am. J. Obst. & Gynec.* 40: 334, August 1940.

This report concerns the successful employment of tattooing with mercury sulfide for the treatment of intractable pruritus caused by leukoplakia-kraurosis, which had not been controlled previously by partial vulvectomy and four additional surgical procedures.

Rehabilitation Following Acute Coronary Occlusion. A. M. MASTER AND S. DACK. *J. A. M. A.* 115: 828, September 1940.

A follow-up study after coronary occlusion was made to determine the incidence and degree of economic restitution and the various factors influencing the latter. Four hundred and fifteen patients were followed for from six months to fifteen years after the attack. There were 185 private and 230 ward patients of all ages, occupations and walks of life.

More than one-half the patients returned to work on full or part time. Half of this group resumed work within three months of discharge, three-fourths within six months and nine-tenths within one year. The percentage of patients returning to work was higher in the younger age groups, particularly those under 40, and in those recovering from an initial attack. The percentage was about the same in males and females. The professional and white collar classes resumed their work more frequently than did persons engaged in other occupations.

The chief cause of failure to return to work was physical disability resulting from angina pectoris, dyspnea and weakness. Other reasons were advice not to work and disability insurance. About one-half the patients who returned to work complained of pain, dyspnea or weakness which were not of sufficient degree to cause disability. It is our impression that the work did not aggravate these symptoms or predispose the patient to them or to further attacks of coronary occlusion or heart failure.

An attack of acute coronary occlusion in itself is not sufficient reason for permanent disability. Complete recovery and full or partial economic restitution are common. Heart failure or a severe anginal syndrome is evidence of complete disability.

Pulmonary Infection and Necrosis in Diabetes Mellitus. S. E. MOOLTEN. *Arch. Int. Med.* 66: 561, September 1940.

The impaired resistance to infection in diabetic persons is probably part of a general vulnerability of diabetic tissues to injury of any type and is related to deficient cellular oxidation. Both cellular repair and immunity responses may be seriously affected.

The unfavorable prognosis of pulmonary tuberculosis in cases of poorly treated diabetes is well known. Other pulmonary infections may also prove disastrous, particularly those which invite suppuration and necrosis. Of peculiar interest is the predisposition of patients with prolonged pancreatic insufficiency to pulmonary suppuration and pulmonary tuberculosis. The former is frequent in cases of congenital steatorrhea associated with fibrosis of the pancreas; the latter, in cases of pancreatic lithiasis.

A case of pancreatic lithiasis is described in which chronic pancreatic insufficiency with diabetes mellitus was complicated by extensive necrotic pneumonia of mixed bacterial type. Only one similar case has been reported in the literature. This type of pneumonia appears to be identical with that described by Letulle and Bezancón under the heading of "dissecting necrotic pneumonia" and differs from other forms of necrotic and suppurative pneumonia in its distinctive morphologic and clinical features. As in the present case, it is probably to be regarded as a special instance of the particular disposition of cachetic tissues to undergo necrosis.

Studies on the Absorption of Sulfanilamide from the Large Intestine: Results Following the Administration of Suppositories. R. TURELL, A. W. M. MARINO AND L. NERB. *Ann. Surg.* 112: 417, September 1940.

The authors have shown that sulfanilamide in solution or in suppository form is absorbed from the rectum and colon in man. Greater absorption followed the rectal administration of sulfanilamide in solution. The results suggest that the colon is a practical site for the administration of sulfanilamide whenever the oral route cannot be utilized. Proctosigmoidoscopic studies following the rectal administration of this drug showed no changes in the normal mucosa of the rectum or colon. Nausea following the administration of sulfanilamide by bowel was observed only once.

Radiation Therapy for Recurrent Sacrococcygeal Cysts and Sinuses. R. TURELL. *Surg.* 8: 469 September 1940.

The author advocated radiation therapy as a substitute for operation for the recurrence of infected sacrococcygeal sinuses. It was pointed out that recurrence characterizes this lesion regardless of the form of surgery utilized, and that recurrences are usually caused by the failure of removal of the primary infected scar tissue and the eradication of infection. The successful treatment of four cases is described. The wounds healed within a period of two months. The quality of scar tissue in each case appeared to be inferior to that observed elsewhere in the body. To date there have been no recurrences following radiation therapy. It is conceivable that when all branches of the sinus and the ectopic epithelium are incompletely removed during the original operation, radiation therapy may fail, and reoperation may become necessary.

Diverticulitis of the Colon with Special Reference to the Surgical Complications. E. E. ARNHEIM. *Ann. Surg.* 112: 352, September 1940.

From 1927 to 1937 thirty-five cases of diverticulitis of the colon were admitted to the surgical services of The Mount Sinai Hospital. Surgical complications were not present in sixteen. The incidence of surgical complications in the remaining nineteen was as follows: peritonitis without perforation in two, abscess in five, perforative peritonitis in five, stenosis (peridiverticulitis) in four, sigmoidovesical fistula in two and associated carcinoma in one. The sigmoid was the most frequent site of the disease, though perforation of a diverticulum of the splenic flexure occurred twice. Operation was not performed in the uncomplicated cases; they subsided under conservative therapy. The operative mortality was 62 per cent.

Roentgen Aspects of Non-Putrid Pulmonary Suppuration. M. L. SUSSMAN. *Am. J. Roentgenol. & Radium Therapy.* September 1940.

Non-putrid pulmonary suppuration differs from simple bronchopneumonia by the occurrence of necrosis of the pulmonary parenchyma. The cases may be grouped into diffuse suppuration without abscess, segmental abscess, and multiple abscesses. About 50 per cent of the cases of non-putrid abscess reach the radiologist when pleural

complications have already occurred which obscure the pulmonary lesions. A roentgenological diagnosis of the underlying abscess is then not possible unless air and fluid are present in the pleural cavity. In this case the presence of a perforated abscess can be inferred.

In a group of 20 cases of non-putrid pulmonary abscess in which fluid levels were shown, 50 per cent showed a single level, 40 per cent numerous levels within a segmental pneumonia, and 10 per cent multiple levels in a diffuse bilateral pneumonitis. This does not give a correct estimate of the incidence of the diffuse disease because many cases are not recognized clinically whether cavitation is present or not. Cavitation is recognized often only by routine serial roentgen examination of cases of mild or moderately severe bronchopneumonia in which resolution is taking place slowly. It is believed that in some cases an infected emphysematous bleb is present rather than a true abscess. Occasionally the abscess cavity persists and is converted into a pseudo-cyst if the inflammatory process subsides.

The bronchial changes which occur regularly in non-putrid pulmonary suppuration are also reviewed briefly.

The Conservative Management of Sigmoidoscopic Perforation. M. A. SALLICK. *Surgery* 8: 473, September 1940.

Perforation of the bowel during sigmoidoscopic examination need not necessarily call for immediate abdominal exploration. The mortality rate in cases operated upon for this complication is high. The fact that the lower colon has usually been thoroughly cleansed prior to the examination makes gross contamination of the abdominal cavity unlikely. The ability of the peritoneum to take care of infection that is not overwhelming deserves consideration. Recovery can occur through the employment of expectant and supportive measures alone. In aged and poor-risk patients with sigmoidoscopic perforation and in cases where there has been a delay of several hours in establishing the diagnosis or in instituting treatment, conservative rather than operative management is advisable.

Syphilis of the Stomach. A Critical Review with Four Additional Cases. A. WINKELSTEIN AND A. CORNELL. *Urol. & Cut. Rev.* 44: 10, October 1940.

Gastric lues, while pathologically rare, is diagnosed clinically frequently. It occurs in the form of masses (gummas) and diffuse infiltration. There is no characteristic clinical picture. It simulates gastritis, ulcer, and carcinoma. A diagnosis should rest on the following criteria: (a) positive Wassermann reaction; (b) lues elsewhere in the body; (c) achlorhydria; (d) extensive and, at times, characteristic radiographs ("dumb-bell" and linitis plastica); (e) response to the therapeutic test; and the best criterion of all (f) resection with histologic proof. Some gastroscopic observations are already at hand. Anti-luetic therapy gives brilliant results in two-thirds of the cases. Surgery is indicated for obstruction and suspicion of neoplasm. Four cases, personally observed and proved by histologic examination, are described. The chief importance of gastric syphilis lies in its differentiation from gastric carcinoma.

BOOK REVIEWS

MIRIAM REINER, M.Sc. *Manual of Clinical Chemistry*. Interscience Publishers, Inc., New York, 1941.

Mimeographed directions were assembled in a booklet for many years and periodically revised for use by the internes and laboratory workers at The Mount Sinai Hospital. It formed the nucleus for this highly useful little volume into which the author attempted to condense all of the more practical and important chemical procedures used almost constantly in clinical investigations carried out in the Chemical Laboratory. By revising and simplifying the directions for the procedures required in performing the various tests, by giving clear-cut instructions for the preparation of reagents, and by providing formulae for simple calculation of results, the author has accomplished the task successfully.

The value of the book is enhanced by tables containing highly useful information concerning chemical constituents of the body fluids, as well as their normal and abnormal values.

Not without interest is also the fact that the book has strong local color. The reviewer notes with pleasure that many well established and useful methods have originated or have been advantageously modified at this hospital.

The book is not only valuable as a guide for laboratory procedures, but is also a useful and very handy source of reference in any laboratory.

I. SNAPPER, M.D. *Chinese Lessons to Western Medicine*. (Foreword by George R. Minot.) Interscience Publishers Inc., New York, 1941.

The experiences of a keen European clinician transferred to China at the peak of his career must supply interesting reading to physicians. This expectation is fully realized in Professor Snapper's new book. Every page reflects the wide scope of his interests and knowledge. Dr. Snapper has long been known as an accomplished clinician and a productive investigator. He details his impressions after several years at the Peiping Union Medical College, emphasizing the differences between the manifestations of disease as seen in the Orient and those observed in the West.

The volume by Dr. Snapper is not easy to review. Its contents are by no means limited to the unique manifestations of disease among the Chinese. The entire field of internal medicine is touched by the author's facile pen. The table of contents reads like a textbook of medicine and in every chapter interesting side-lights are presented. One is impressed by the fact that there must be important factors which alter the response of the Oriental to diseases which we know in the West. The author makes out a strong case for the preponderant influence of diet and dietary deficiencies in determining clinical pictures. His facts about the low protein content of the Chinese diet, its high content of unsaturated fats, its relative freedom from animal proteins, cholesterol and dairy products and its low vitamin content are presented to prove that these influence the manifestations of almost every clinical picture in China.

Every student of clinical medicine can read this book with profit. From it he will learn some of the lessons that the title promises and will realize that only a teacher like Dr. Snapper could himself have learned so much.

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CONTENTS

	PAGE
DESOXYCORTICOSTERONE. <i>George W. Thorn, M.D.</i>	1177
SOME CLINICAL OBSERVATIONS UPON THE METABOLISM AND UTILI- ZATION OF PROGESTERONE; THEIR APPLICATIONS TO GYNECIC PRACTICE. <i>E. C. Hamblen, M.D.</i>	1200
PAINFUL LESIONS OF THE FEET. <i>Seth Selig, M.D.</i>	1216
ASEPTIC INFARCTION OF THE KIDNEY. <i>Gordon D. Oppenheimer, M.D.</i>	1220
DIFFERENTIAL DIAGNOSIS OF SOLITARY CYSTIC AREAS IN BONE. <i>Edgar M. Bick, M.D.</i>	1225
INCIDENCE OF HYPERTENSION IN PEOPLE OF FORTY YEARS OF AGE AND OLDER. <i>Arthur M. Master, M.D., and Simon Dack, M.D.</i> ..	1232
CLINICAL NEUROPATHOLOGICAL CONFERENCE.....	1236
THE STORY OF THE MOUNT SINAI HOSPITAL: THE FORMATIVE YEARS, 1852-1872, I.	1239
OBITUARIES.....	1248
ABSTRACTS.....	1250
INDEX OF VOLUME EIGHT.....	1253

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DESOXYCORTICOSTERONE¹GEORGE W. THORN, M.D.²*[Associate Professor of Medicine, Johns Hopkins University]*

INTRODUCTION

Thomas Addison's description in 1855 of a clinical syndrome which resulted from destruction of the adrenal glands first called attention to the vital function of these organs. Shortly thereafter Brown-Sequard demonstrated conclusively that complete removal of both adrenals was followed promptly by death of the experimental animal. The studies of Vulpian, Oliver, Schaeffer, Abel, Takamine and Aldrich ultimately resulted in the isolation of epinephrin from the adrenal medulla. It was soon noted clinically, however, that epinephrin was ineffective in the treatment of Addison's disease. Furthermore, it was observed experimentally that the complete removal of one adrenal, accompanied by destruction of the medulla of the remaining adrenal, did not give rise to the classical signs and symptoms of adrenal insufficiency. From these observations it appeared that the "life-maintaining" substance liberated by the adrenal was derived from the cells of the cortex.

In 1927 Hartman, MacArthur and Hartman (1), and Rogoff and Stewart (2) independently reported the preparation of adrenal cortical extracts which were capable, on injection, of prolonging the survival period of adrenalectomized animals. In 1930, Swingle and Pfiffner (3), and Hartman and Brownell (4) described methods of preparing adrenal cortical extracts of much greater potency. These extracts appeared to be capable of maintaining bilaterally adrenalectomized dogs and cats in good condition for prolonged periods. It was also noted that injections of these extracts in adequate quantities resulted in considerable improvement in patients with Addison's disease (5, 6). However, difficulties which were encountered in the preparation of large quantities of potent extract and in the standardization of the hormone, in addition to the high cost of preparation, greatly limited adequate clinical trial. Furthermore, it was apparent at this time that although improvement might be made in the methods of extracting hormone from adrenal glands, it was doubtful whether the preparation of hormone from this natural source could ever provide an adequate quantity of potent material at a cost which most patients could afford.

The classical studies of Loeb (7) and Harrop (8) demonstrated the beneficial effect of sodium salts in the treatment of patients with Addison's

¹ Lecture delivered at the Blumenthal Auditorium of The Mount Sinai Hospital on March 14, 1941, as part of a Symposium on the Steroid Hormones.

² It was originally planned to publish this paper in the Anniversary Volume of this Journal (Vol. 8, No. 5, 1942) dedicated to Dr. Bernard S. Oppenheimer.

disease. Not only was a diet of high sodium content beneficial but the studies of Truszkowski and Zwemer (9) and Wilder (10) demonstrated the advantages of a low potassium intake in patients with adrenal insufficiency. From these observations it was evident that in the clinical evaluation of adrenal cortical hormone therapy the mineral content of the diet required great consideration.

In 1933 both Kendall (11) and Grollman (12) obtained crystalline material from adrenal cortical extracts. This material appeared to possess cortical hormone-like activity. Somewhat later Reichstein (13) isolated a crystalline compound from the adrenal cortex which possessed cortical hormone-like activity and which he identified and named "*corticosterone*." Subsequently Kendall demonstrated that the active compound which he had described was identical with that of Reichstein's "*corticosterone*" (14). In 1937 Steiger and Reichstein (15) announced the synthesis from *stigmasterol* of a steroid compound, *desoxycorticosterone acetate*. This compound was found to possess cortical hormone-like activity (16) and was noted to be very closely related, chemically, to progesterone. During the following year Reichstein and Von Euw (17) succeeded in isolating *desoxycosterone* from adrenal cortical extract, thus establishing its natural occurrence. It is unique that in this instance a hormone was synthesized prior to its isolation from a natural source. At the present time it is feasible commercially to prepare *desoxy-corticosterone acetate* from cholesterol at a cost which most patients are able to afford.

INTERMEDIATE METABOLISM OF ADRENAL CORTICAL HORMONE

Few data are available regarding the nature of the intermediate metabolism of the adrenal cortical hormone in man. From 1000 liters of human male urine Engel (18) isolated 63 mg. of *pregnandiol-3(α)*, 20 (α), 68 mg. of *trans-dehydroandrosterone*, 167 mg. of *androsterone* and 27 mg. of *etiocholanol-3(α)-one-17*.

Callow and Callow (19) have suggested that since *trans-dehydroandrosterone* is excreted in increased amounts in the urine of a eunuch, this compound may be of adrenal cortical origin. This is consistent with the observation that normal females as well as castrate females excrete this compound in an amount comparable with that excreted by normal males. Additional evidence bearing on this point is provided by the observation of Crooke and Callow (20) that there is an increased excretion of *trans-dehydroandrosterone* in patients with adrenal cortical tumors.

Androsterone and *etiocholanol-3(α)-one-17* are also constituents of the urine of normal males, castrate males, normal females, and castrate females, although the amounts excreted by the castrate male are significantly smaller (0.6 mg. of *androsterone* and 0.9 mg. of *etiocholanol-3(α)-one-17* per liter) than those excreted by the normal male. In addition, Marker and

Lawson (21) have isolated androsterone from the urine of pregnant women, and Butler and Marrian (22) have obtained etiocholanol-3(α)-one-17 from the urine of a woman suffering from adrenal hyperplasia. The observation of Callow (23) and Dorfman, Cook, and Hamilton (24) that the injection of massive doses of testosterone in male patients suffering from hypogonadism is followed by an increased excretion of androsterone and etiocholanol-3(α)-one-17 suggests that in part, at least, these compounds are of gonadal origin and indicates that the reduction of testosterone can take place in some site other than the testis.

Further evidence on this point has been obtained by Dorfman and Hamilton (25) who observed an increased amount of androsterone in the urine of a eunuchoid patient following the oral administration of *testosterone*, androsterone, androstenediol-3(α),17, androstenedione-3,17, and androstene-4-dione-3,17.

TABLE 1

A summary of the excretion of certain neutral steroids which have been isolated from human urine

	TRANSE- HYDRO- ANDROS- TERONE	ANDROS- TERONE	ETIOCHOL- ANOL-3- ONE-17	ETIOALLO- CHOLANOL- 3(β)-ONE-17	PREG- NANDIOL
Normal male.....	+	+	+	+	+
Normal female.....	+	+	+	+	+
Castrate male.....	+	+	+		
Castrate female.....	+	+	+		+
Pregnant female.....		+			+
Adrenal hyperplasia.....		+	+	+	
Adrenal carcinoma.....	+				

Butler and Marrian (22) have also isolated etioallocholanol-3(β)-one-17 (isoandrosterone) from the urine of a woman with adrenal hyperplasia and Hirschmann (26) isolated isoandrosterone from the urine of a 27 year old woman with virilism. Pearlman (27) was able to isolate 11 mg. of isoandrosterone from 146 liters of normal female urine and Dorfman (28) recovered the compound (approx. 3 mg. daily) from the urine of a hypogonad male who was receiving 30 mg. of testosterone daily by injection. Thus, although isoandrosterone has been isolated from the urine of women with virilism as well as from the urine of normal females its recovery in higher concentrations from the urine of a patient treated with testosterone (28) suggests that this compound may also in part at least be of gonadal origin.

Pregnanediol-3(α),20(α) is generally recognized as a normal constituent of gravid and non-gravid human female urine. The isolation by Engel (18) of *pregnanediol-3(α),20(α)* from human male urine and the studies of Buxton (29) in which pregnanediol was isolated from the urine of a normal male subject following the injection of progesterone suggest that the human

male is able to effect the reduction of progesterone to pregnandiol. Marker, Wittle, and Lawson (30) have isolated pregnandiol-3(α),20(α), allo-pregnandiol-3(α),20(α), and *allopregnandiol*-3(β),20(α) from bull urine but no traces of the pregnandiols could be obtained from steer urine (31). Beall (32) was able to isolate progesterone and *allopregnanol*-3(β)-one-20 from ox (steer) adrenal glands. This would suggest that in this species the testis may play some role in the reduction of progesterone to the pregnandiols and that in the absence of the testis the degradation proceeds to unrecognizable products. In this connection it is interesting to note that no pregnandiols could be recovered from the urine of the pregnant rhesus monkey following the injection of progesterone or pregnandiol (33).

The presence of androsterone, trans-dehydroandrosterone, etiocholanolone in the urine of castrate males, castrate females and patients with adrenal cortical hyperplasia or tumor, suggests the possibility that these substances may actually represent excretion products of adrenal cortical hormone.

PHYSIOLOGICAL CONSIDERATIONS

The regulation of the renal excretion of sodium, chloride and potassium represents the most striking activity of desoxycorticosterone. During a period of hormone administration sodium and chloride excretion are greatly reduced, whereas the excretion of potassium is facilitated (Chart 1 and table 2). This effect of the hormone has been observed in normal dogs (16) and in normal human subjects (34) as well as in bilaterally adrenalectomized dogs (16) and patients with Addison's disease (35). Renal clearance studies in normal dogs reveal the fact that the clearance for sodium and chloride is markedly reduced during hormone administration whereas creatinine clearance (a measure of glomerular filtration in dogs) is not affected appreciably (chart 2). These observations suggest that the synthetic hormone exerts a specific effect on the tubular reabsorption of sodium and chloride, an observation which Harrison and Darrow (36) have made with respect to aqueous adrenal cortical extracts, tested in adrenalectomized animals.

Associated with the retention of sodium and chloride which occurs during desoxycorticosterone administration there is a striking increase in plasma volume (chart 3) with a corresponding decrease in hematocrit (per cent volume of red cells) (35). It cannot be stated conclusively at this time whether the increase in plasma volume merely reflects the effect of the hormone in increasing the renal tubular reabsorption of sodium and chloride or whether, in addition, the hormone may exert a specific effect upon the permeability of blood vessels. Closely correlated with the increase in plasma volume is the striking expansion in the volume of extra-vascular-extra-cellular fluid. So marked is this increase that one of the

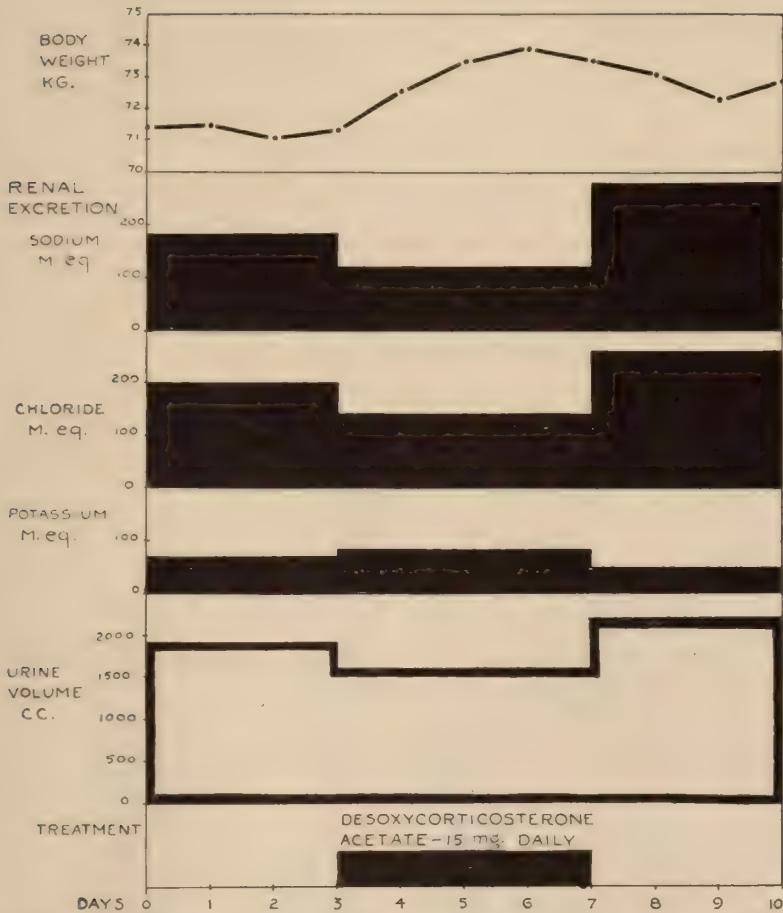


CHART 1. The effect of desoxycorticosterone acetate treatment in a normal subject. (After Thorn and Emerson, 1940, by courtesy of the Annals of Internal Medicine.)

TABLE 2

The effect of desoxycorticosterone acetate treatment on the renal excretion of sodium, chloride and potassium in a normal male dog

24 HOUR PERIOD	URINE VOLUME	SODIUM	CHLORIDE	POTASSIUM	TREATMENT
	cc.	m. eq.	m. eq.	m. eq.	
Control.	500	60.0	58.8	16.8	1 mg. of desoxycorticosterone acetate
Treated.	525	41.4	49.1	21.4	
Control.	715	71.6	66.8	16.9	

earliest signs of excessive hormone administration is the appearance of generalized pitting edema.

In prolonged adrenal insufficiency as a consequence of excessive excretion

of sodium and chlorides and retention of potassium and nitrogen (7, 8, 9, 10) characteristic changes in blood chemistry are observed, i.e., a lowered concentration of sodium and chloride in serum and an increase in the concentration of potassium and non-protein nitrogen. Treatment with desoxycorticosterone corrects these changes. However, an interesting phenomenon is not infrequently observed in relation to the changes in serum concentration of sodium and chloride during the early period of hormone therapy. Due to the marked expansion of plasma and extra-cellular fluid volume which occurs at this time, the serum concentration of sodium and chloride may fail to rise (chart 4) and, in unusual instances,

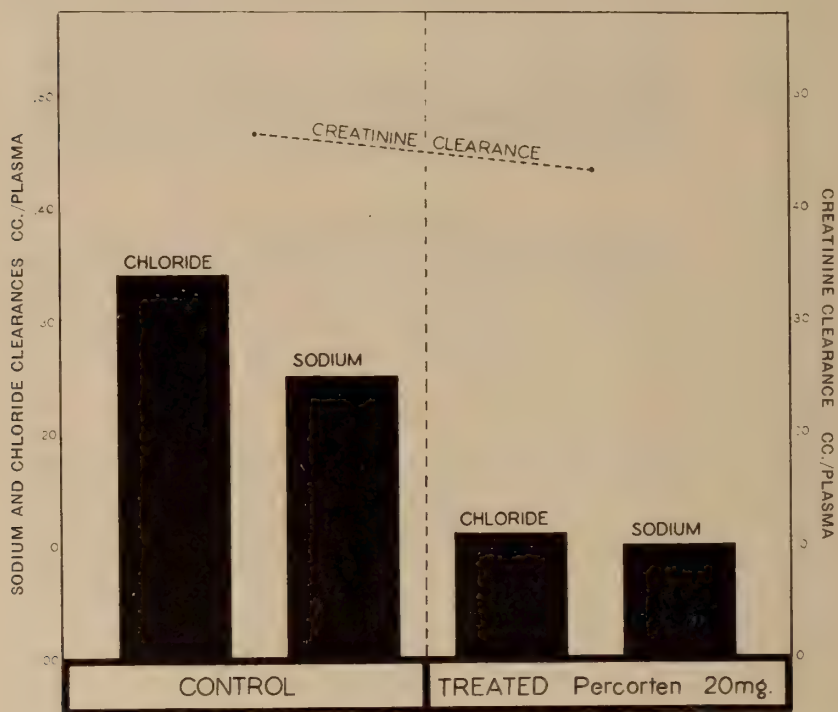


CHART 2. The effect of desoxycorticosterone acetate therapy on sodium and chloride clearance—normal dog.

may actually fall slightly during this period. These changes are particularly likely to occur in the presence of a limited sodium and chloride intake. Thus despite the presence of a positive sodium and chloride balance at this time one may observe temporarily a failure of sodium and chloride concentration to be restored to normal. If plasma volume measurements are made during this period it may be readily demonstrated that the total plasma content of sodium however, has been increased appreciably (chart 4).

Under certain circumstances it appears that as experimental animals and

patients slowly develop insufficiency and slowly lose sodium and chloride, a comparable decrease in plasma volume and extra-cellular fluid volume may occur. This decrease in plasma volume assists greatly in maintaining a relatively normal serum concentration of sodium and chloride. Under these conditions there is a lack of correlation between the normal serum concentration of sodium and chloride and the evident clinical signs and symptoms of insufficiency. When desoxycorticosterone is administered to an animal or patient in this situation, one may observe first a temporary decrease in the serum concentration of sodium and chloride, particularly

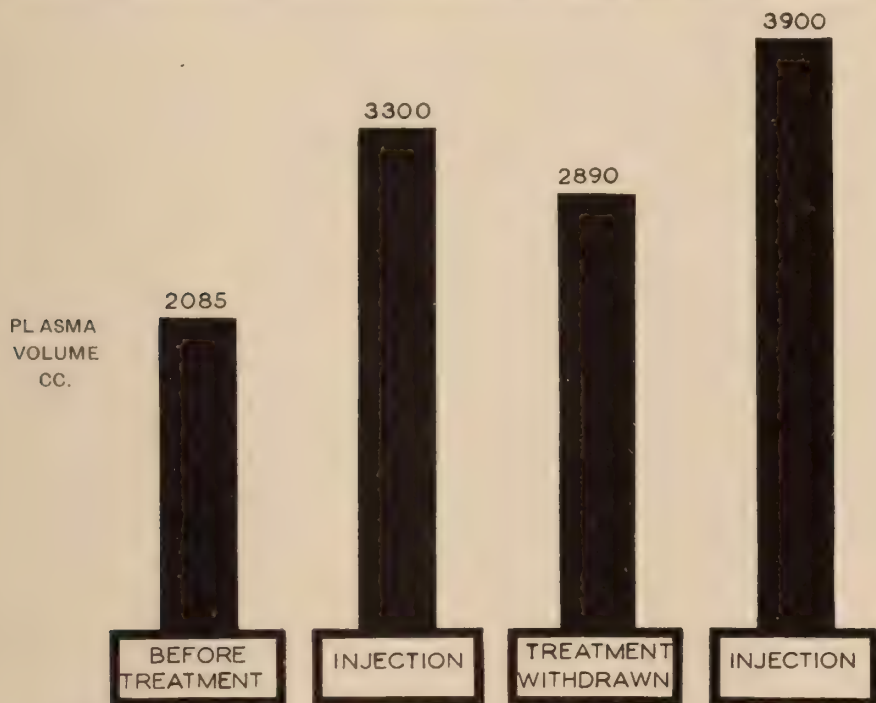


CHART 3. The effect of desoxycorticosterone acetate therapy (intramuscular injections) on plasma volume (Addison's disease). (After Thorn and Firor, 1940 by courtesy of the Journal of the American Medical Association.)

if the diet contains relatively little sodium chloride. Under these circumstances it appears that the striking increase in extra-cellular fluid volume has exceeded the ability of the body to maintain a normal concentration of sodium and chloride. Balance experiments in patient D. B. (37) indicated that the expansion in extra-cellular fluid volume which occurred in this patient greatly exceeded the volume of water which had been made available as the result of a positive water balance. It thus appeared probable that water had been liberated from cells to permit expansion of the extra-cellular fluid volume. The greatly increased excretion of potassium which was noted during this period and which could not be accounted for by a

reduction in potassium concentration in serum and, presumably, extra-cellular fluid compartment, substantiated the possibility of this fluid shift from cells to extra-cellular compartment. From these studies in which expansion of extra-cellular and plasma fluid volume exceeded temporarily

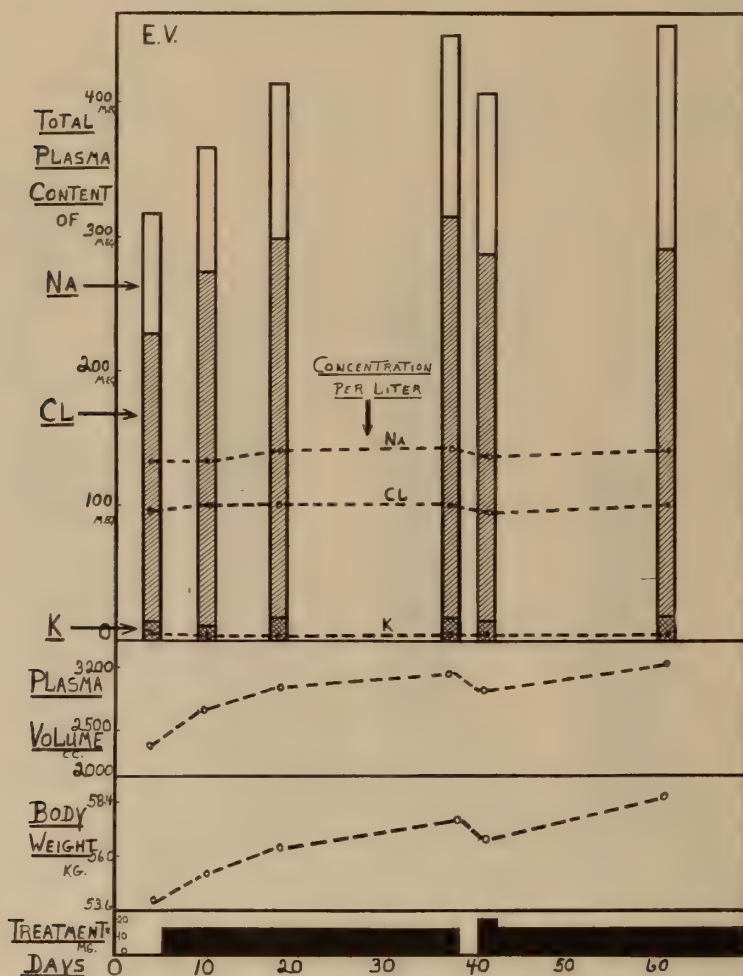


CHART 4. The effect of desoxycorticosterone acetate treatment on the concentration and total quantity of plasma sodium, chloride, and potassium. (After Thorn, Howard and Emerson, 1939, by the courtesy of the Journal of Clinical Investigation.)

at least the retention of sodium and chloride; and from the fact that the great increase in volume of extra-cellular fluid could be accounted for only in part by a reduction in urine volume, it would appear that desoxycorticosterone directly or indirectly, exerts an effect on cells other than those of the renal epithelium.

At least four factors may contribute to the hypotension which is observed in adrenal insufficiency, i.e., marked reduction in plasma volume, impaired heart action, anemia and alterations in the peripheral vascular response. Although desoxycorticosterone administration is followed by a rapid rise in blood pressure from shock levels, complete restoration to normal levels may require weeks of continued therapy. No doubt the rapid increase in plasma volume contributes to the early rise in blood pressure which is associated with hormone therapy, and, it is possible, that further expansion of the vascular bed during succeeding days of therapy and an increased circulatory rate may account for the lack of correlation between the rapid restoration of plasma volume and the much slower response of blood pressure. That factors other than plasma volume are concerned with the effect of desoxycorticosterone treatment on blood pressure is suggested by the rapidity with which moderate degrees of hypertension are attained in some patients with approximately normal plasma volumes whereas the blood pressure of other patients with normal plasma volumes fails to exceed normal levels despite long continued therapy (38, 39).

It has been demonstrated repeatedly, that treatment with desoxycorticosterone will maintain the life of bilaterally adrenalectomized animals and patients with Addison's disease without regard to the mineral composition of the diet (16, 35, 38, 40), although it is evident that desoxycorticosterone does not contain all of the factors which are attributed to the adrenal cortex (41). Experiments clearly indicate that desoxycorticosterone does not possess the "carbohydrate-regulating" property (chart 5) which is possessed by certain aqueous adrenal cortical extracts and crystalline adrenal cortical compounds which contain an oxygen atom on C₁₁, i.e., corticosterone, dehydrocorticosterone and 17-hydroxycorticosterone. Patients with Addison's disease under treatment with desoxycorticosterone acetate do not develop hypoglycemia as long as they ingest and absorb adequate quantities of readily available carbohydrate at relatively frequent intervals. However, when outside sources of carbohydrate are not available, such animals or patients may readily develop hypoglycemic symptoms (42). It has been demonstrated that desoxycorticosterone acetate is ineffective in the restoration of carbohydrate reserves from non-glucose sources (43).

One group of observations concerning the relationship of desoxycorticosterone to carbohydrate metabolism needs amplification. It has been noted (42) that the blood glucose levels following the oral administration of glucose frequently rose higher in patients who had received long-continued desoxycorticosterone acetate therapy, than in control tests made prior to therapy (chart 6). The blood glucose curve following intravenously administered glucose did not change significantly during the period of therapy. Since in all instances these changes were observed in patients who had made

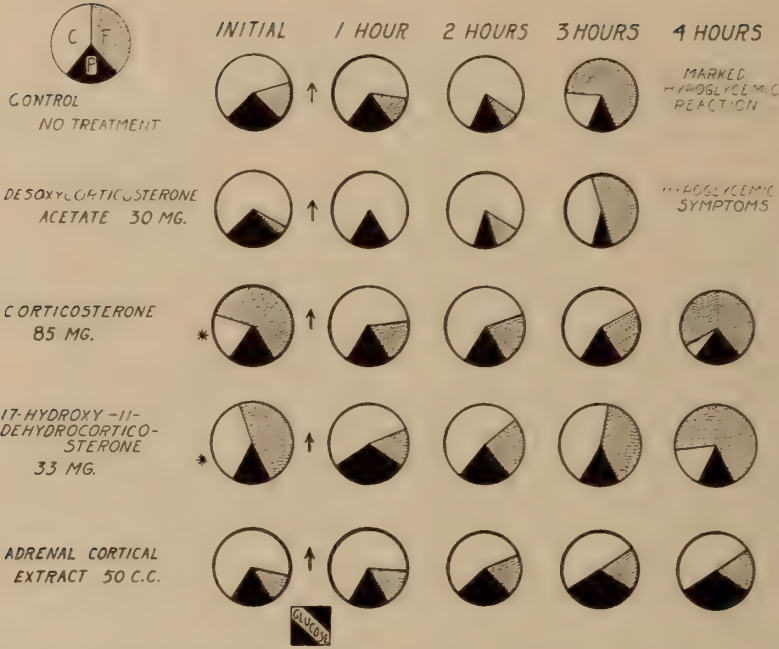


CHART 5. Caloric changes following intravenous glucose (Addison's disease, E. L.). (After Thorn, Koepf, Lewis and Olsen, 1940, by courtesy of the Journal of Clinical Investigation.)

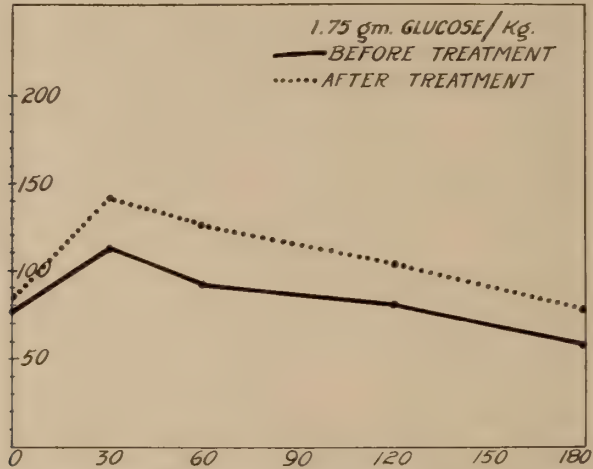


CHART 6. The effect of long continued desoxycorticosterone acetate therapy on the gastrointestinal absorption of glucose in patients with Addison's disease.

striking clinical improvement, it was assumed that the improvement in glucose absorption which had occurred during desoxycorticosterone acetate therapy was related to the improved state of circulation and the generally

improved clinical condition of the patient rather than to a specific effect of the hormone on the intestinal absorption of glucose. It is of course possible that the latter consideration may be true, although to date no convincing evidence on this point has been presented.

In studies in which the work performance of adrenalectomized animals was measured, Ingle (44) noted that although desoxycorticosterone acetate treatment was followed by a striking increase in total work performance, treatment with this compound did not restore the level of performance of adrenalectomized animals to that of normal controls. Adrenal cortical compounds with an oxygen atom on C₁₁ were in general much more potent in this respect.

Although desoxycorticosterone acetate administration will induce atrophy of the adrenal cortex in normal animals this compound is much less potent in this respect than adrenal cortical extract and certain other adrenal cortical steroids (45). Kuhlman (46) administered a daily dose of 25 mg. of desoxycorticosterone acetate to normal dogs for prolonged periods, and observed no symptoms of adrenal insufficiency upon withdrawing hormone therapy. It has also been observed that desoxycorticosterone acetate therapy is less efficacious than adrenal extract and other adrenal cortical steroids in causing thymus involution in adrenalectomized animals (45).

It thus appears that although desoxycorticosterone lacks certain known attributes of the adrenal cortex, its potency in maintaining the life of adrenalectomized animals and patients with Addison's disease may be explained on the basis of its ability to restore electrolyte balance, hydration and blood pressure. The correction of these abnormalities appears to be sufficient, in most instances, for the maintenance of a relatively good state of health in the absence of unusual conditions of stress or infection.

METHODS OF ADMINISTERING DESOXYCORTICOSTERONE ACETONE

At present three methods of administering desoxycorticosterone acetate are known to be feasible i.e. intramuscular injection of hormone in oil (35, 38, 39, 40), subcutaneous implantation of pellets of crystalline hormone (39) and the sublingual administration of a solution of desoxycorticosterone acetate in propylene glycol (47, 48). Some experimental evidence exists (48, 49) indicating that the hormone is absorbed when administered as an inunction. However, this latter technique has not as yet been standardized sufficiently to justify its use in the treatment of patients with severe adrenal cortical deficiency. Hormone administered orally and in rectal suppositories has also been attempted (48). These latter methods are relatively ineffective and the cost of hormone therapy administered by either of these methods would be prohibitive at the present time for most patients.

In considering the three methods of administration which are feasible,

certain facts are evident. The ratio of hormone required by the three methods is as follows: pellets 1.0 mg.; intramuscular injection 1.3 mg.; sublingual 5.0 mg. Pellet implantation is the most efficient method of therapy and, of course, obviates the necessity for daily injections of hormone. This method requires surgical implantation once in 12 to 15 months which must be preceded by a very carefully conducted assay period (hormone in oil) to determine exactly the number of pellets which are required.

The method of intramuscular injection presents the difficulties which are encountered when subcutaneous or intramuscular administration is required over a period of years. However, one injection per day suffices and the dose of hormone can be easily regulated. Occasionally, local reactions to the oil in which the hormone is dissolved necessitates a change in the method of administration.

Sublingual administration of hormone obviates the necessity for injections or implantations. However, it appears that in order to be most

TABLE 3

Relative cost of desoxycorticosterone acetate therapy for a patient requiring 3 mg. of Percorten daily

TYPE OF THERAPY	HORMONE REQUIREMENT PER DAY	APPROXIMATE COST PER YEAR
	mg.	
Pellets.....	2.3	\$120
Percorten.....	3.0	\$160
Sublingual.....	11.5	\$600

effective the hormone must be administered in small doses, 4-6 times daily. In addition, the increase in hormone requirement which is necessary when this method of administration is employed greatly increases the cost of treatment (Table 3). It seems apparent at the present time that any method of administration which ensures an adequate and relatively constant level of hormone in the body tissues will prove successful. The severity of the disease, the patient's financial status, his willingness to take a daily hypodermic injection or his ability to cooperate by taking hormone sublingually several times daily will be determining factors in the method of administration which is finally selected.

The advisability of implanting pellets of crystalline desoxycorticosterone acetate may be considered after a patient has been maintained in good condition for a period of 4 to 8 weeks with daily injections of hormone in oil (*Percorten*). The number of pellets which is required is calculated directly from the minimum quantity of *Percorten* which will maintain the patient in good condition. For each 0.5 mg. of *Percorten*, one pellet of 125 mg. is implanted. The daily maintenance dose of *Percorten* is

administered in conjunction with a constant quantity of sodium chloride tablets, 3 to 5 gm. (enteric coated) administered with food. The added sodium chloride medication during the assay period and following pellet implantation provides a convenient means of balancing any excess of hormone from pellets by merely reducing or discontinuing the 5 gm. of sodium chloride medication. If the assay is carried out carefully over a period of 4-8 weeks it is rarely necessary to remove pellets because of symptoms of overdosage. In the event that signs of overdosage do become manifest following pellet implantation it is usually possible to correct the situation by:

- 1) Withdrawing the added sodium chloride medication;
- 2) Providing a diet of low sodium chloride content;
- 3) Administering potassium citrate solution (10 per cent solution in fruit juices).

A single implantation of pellets, weighing 125 mg. each, provides effective therapy in most patients for a period of 12-15 months. Toward the end of this period it is advisable to resume sodium chloride medication, followed later by Percorten injections as indicated by changes in body weight, strength and blood pressure. When the new level of Percorten administration has been carefully determined, a second implantation of pellets may be performed.

EFFECTS OF THERAPY

A. Changes in body weight. A change in body weight constitutes one of the most sensitive indications of a change in the clinical state of a patient with Addison's disease. Improvement in clinical condition is accompanied regularly by weight gain and a relapse is associated almost invariably with weight loss (35). A significant increase in body weight is observed in most patients within 48 hours after desoxycorticosterone acetate therapy is instituted. Failure to gain weight indicates insufficient therapy; whereas, rapid weight gain suggests excessive therapy. Withdrawal of treatment results in a prompt and progressive decrease in weight which is usually followed by decreased muscular efficiency, loss of appetite and the onset of symptoms of adrenal insufficiency. Sudden changes in weight in these patients appear to be directly related to alterations in mineral and water balance. More gradual weight increments may be observed during long continued therapy and reflect the effect of the general improvement in appetite and sense of well being.

B. Changes in blood pressure. A marked increase in blood pressure is observed in nearly all patients with Addison's disease who are treated with desoxycorticosterone acetate (39). Particularly noteworthy is the appreciable rise in diastolic pressure. It is of interest to note that in most cases there occurs first a considerable increase in plasma volume unaccompanied by any significant rise in blood pressure unless the patient is in a

crisis. Later, in two to eight weeks, a rise in blood pressure is noted. In most patients, a moderate rise in blood pressure is associated with evidence of marked clinical improvement. In some instances, however, hypertensive levels may be attained without complete restoration of patients to normal activity (38, 39, 40).

C. *Changes in cardiac diameter.* It is well known that the heart is small in patients with Addison's disease (50). The changes in cardiac

TABLE 4
Changes in cardiac diameter—46 patients

	HEART: CHEST RATIO
	per cent
Prior to treatment.....	38.6
Maximum measurement during treatment.....	42.2
Present status.....	41.3

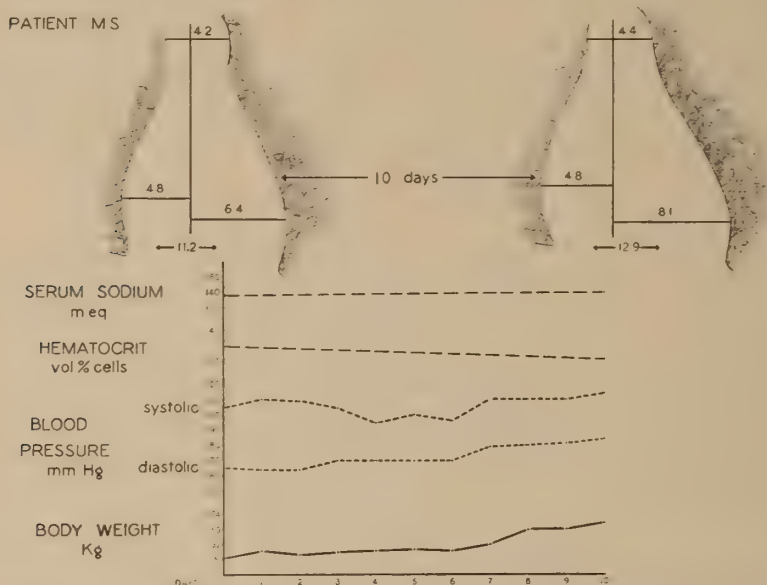


CHART 7. Changes in cardiac diameter as a result of desoxycorticosterone acetate therapy (Addison's disease).

diameter which may occur during synthetic hormone therapy have been reported by Ferrebee and his associates (38) and by McGavack (51). It should be noted that excessive cardiac enlargement rarely occurs unless excessive doses of hormone and sodium chloride are administered or unless organic heart disease complicates Addison's disease. Thus, in 46 patients treated in the Johns Hopkins Hospital during the past two years the heart:chest ratio increased only slightly during a period of prolonged therapy (Table 4). However, in two patients signs and symptoms of

early congestive heart failure were noted during the course of therapy. In both of these patients there was evidence of pre-existing organic heart disease. Adrenal insufficiency may so reduce the cardiac load that detection of organic heart disease may be extremely difficult in the untreated state. Cardiac measurement should be followed very carefully in all patients receiving desoxycorticosterone acetate therapy (chart 7). Excessive cardiac enlargement and/or an increase in venous pressure are urgent indications for an immediate reduction in the dose of hormone and for keeping the patient at total bed rest.

TABLE 5

Summary of desoxycorticosterone acetate therapy (pellets) in Addison's disease

Number of patients.....	113
Number of pellets per patient.....	7 (mean)
Total quantity of hormone per patient.....	880 mg. (mean)
Duration of desoxycorticosterone acetate treatment.....	17 months (mean)
Mortality rate.....	12.8%
Mortality rate per year of therapy.....	9.2%

TABLE 6

Causes of death in 7 patients with Addison's disease treated with implantation of pellets (Johns Hopkins Hospital)

2—Streptococcus pharyngitis and pneumonia
1—Renal tuberculosis
1—Pericarditis
1—Coronary thrombosis ? (age 70)
1—Hypoglycemia
1—Anaphylactic reaction

SUMMARY OF DESOXYCORTICOSTERONE ACETATE PELLET THERAPY IN ADDISON'S DISEASE

During the past two years, 54 patients with Addison's disease have been treated with desoxycorticosterone acetate in the Johns Hopkins Hospital. Of this number, 50 received pellet implantations. In addition, with the cooperation of physicians elsewhere, pellets have been supplied to 63 other patients, making a total of 113 patients who have been treated by means of pellet implants (Table 5). The average duration of therapy for the 50 patients in the Johns Hopkins Hospital who have received pellet implantations now exceeds 2 years. During this period 7 patients (14 per cent) have died (Table 6). The mortality rate per year of therapy has thus been 7 per cent. At the present time the condition of the 43 remaining patients may be classified as follows: very good—7; good—20; fair—12 and poor—4. Of the group of 50, 27 were males; of the 23 male patients who now survive, 14 or approximately 60 per cent are regularly employed.

COMPLICATIONS WHICH MAY ARISE DURING DESOXYCORTICOSTERONE
ACETATE THERAPY

In two patients, intramuscular injections of desoxycorticosterone acetate in sesame oil (Percorten) were accompanied by localized redness, pain and tenderness at the site of the injection, as well as fever and malaise. It was subsequently demonstrated that these reactions were due to the injection of oil and not to synthetic hormone. Both patients did well when pellets of synthetic hormone were implanted.

On two occasions in over 200 pellet implantations, pellets have been extruded subsequently from the site of the incision. Such a complication may be avoided by placing the pellets a distance of at least 2.5 cm. from the margin of the incision.

TABLE 7

Signs and symptoms associated with excessive retention of sodium

1. Edema, headache
2. Hypertension
3. Cardiac enlargement
4. Neuromuscular pain
5. Muscular weakness
6. Paralysis

TABLE 8

Serum potassium:sodium ratio

TREATMENT	SERUM K	SERUM Na	K:Na
	<i>m.eq./l.</i>	<i>m.eq./l.</i>	
Untreated.....	8.0	120	1:15
Adequate.....	4.6	140	1:30
Excessive.....	3.2	145	1:45

Most of the complications which arise during the course of desoxycorticosterone acetate appear to be due to excessive doses of hormone and sodium chloride which result in the retention of excessive quantities of sodium and chloride (Table 7) and in a profound disturbance in the Na/K ratio (Table 8).

Edema, associated with headache, is the most common accompaniment of excessive therapy. This complication is most likely to occur during the early weeks of treatment when an attempt is being made to determine the patient's optimum maintenance dose of hormone. The edema subsides rapidly following reduction in the dose of hormone and/or a reduction in sodium chloride intake.

Hypertension may be observed after treatment has been continued for some time. In patients with Addison's disease in whom some degree of hypertension existed prior to the onset of adrenal insufficiency there is

a great predilection for the blood pressure to return to a high level with minimum doses of hormone. The elevation in blood pressure can be controlled in practically all cases by reducing the dose of hormone and by restricting sodium chloride intake.

Occasionally after a continued period of hormone therapy during which there has been a considerable increase in plasma volume, body weight, blood pressure and physical activity, dyspnoea, associated with signs of pulmonary edema, may become manifest. This complication is most likely to occur in older patients or in patients in whom there has been some evidence of pre-existing myocardial damage or vascular disease. This complication may be avoided if care is exercised in regulating the dose of hormone and in restricting physical activity during the period in which blood volume, blood pressure and body weight are increasing. Treatment consists in absolute bed rest, digitalization, immediate withdrawal of all sodium chloride therapy, restriction of sodium chloride in the diet and a reduction in the dose of hormone. Subsequent rehabilitation should proceed very slowly.

The continued administration of excessive quantities of desoxycorticosterone acetate and added sodium chloride may result in an abnormal lowering of the serum concentration of potassium. This is particularly likely to occur if large quantities of dextrose solution are being given simultaneously. On two occasions an abnormal lowering of the serum concentration of potassium in one of our patients was associated with muscular weakness and transient paralysis involving the extensor muscles of the neck, hands and feet. This patient had been given large quantities of the synthetic compound (25 mg. daily) in addition to intravenous sodium chloride and dextrose solutions in preparation for a nephrectomy. The abrupt onset and transient nature of the paralysis as well as the complete recovery suggest an analogy between these episodes and those noted in patients with familial periodic paralysis in which the serum potassium level has also been observed to be low during an attack. Recent examination of this patient revealed no evidence of muscular weakness. Kuhlman (46) and associates have observed weakness and paralysis in normal dogs treated for a long period with a large dose of desoxycorticosterone acetate (25 mg. daily).

Of much more common occurrence, however, are the vague neuromuscular pains, noted in patients who have received excessive hormone and sodium chloride. Frequently these pains are referred to the joints, and not infrequently a considerable degree of contraction of the tendons of the thighs may be observed. It is possible that the pain and disturbance in function may be related to a high tissue content of sodium, since Turner and Buell (52) recently have observed extremely high sodium values in tissues of both normal and adrenalectomized animals which have been treated with a moderate excess of desoxycorticosterone acetate. In

clinical therapy these untoward effects may be obviated by careful regulation of the dose of hormone and by arranging a diet which is relatively high in foods rich in potassium, i.e., meat, bananas, prunes. If necessary 20 to 40 cc. of a 10 per cent solution of potassium citrate may be administered.

Hypoglycemia is one of the most important complications which may arise in patients treated with desoxycorticosterone. Large doses of adrenal cortical extract will correct this abnormality in carbohydrate metabolism (53), but this form of therapy over any extended period is not feasible for most patients. Considerable benefit may be derived from a diet relatively high in carbohydrate content, and by insisting upon frequent feedings. The late night feeding, in particular, should contain a mixture of carbohydrate, fat and protein. During the course of infections or under conditions of stress and strain, hypoglycemia should be combated vigorously (54). Until a compound which possesses "carbohydrate-regulating" potency is synthesized, there is little hope of satisfactorily correcting the predisposition to develop hypoglycemia which a large proportion of patients exhibit.

The close chemical relationship which exists between desoxycorticosterone and progesterone suggests that desoxycorticosterone acetate treatment might possibly result in progestational changes in female patients with Addison's disease. To date, however, no abnormality in the menstrual cycle has been observed as the result of treatment with the synthetic adrenal cortical hormone. In several patients increased turgor of the breasts has been noted after continued treatment. It appears probable that this change may be accounted for in part at least by the increased accumulation of extracellular fluid.

EFFECTIVENESS OF DESOXYCORTICOSTERONE ACETATE THERAPY IN SUPPORTING PATIENTS WITH ADDISON'S DISEASE DURING THE COURSE OF INTERCURRENT INFECTIONS AND DURING MAJOR OPERATIVE PROCEDURES

Several of the patients reported in this series have recovered promptly from acute upper respiratory tract infections as well as from infections of the urinary tract. One patient recovered from lobar pneumonia (pneumococcus). Hick (55) also reports the "rapid recovery from type XIII lobar pneumonia treated with rabbit serum of a patient with Addison's disease under treatment with desoxycorticosterone acetate." In the treatment of streptococcus infections to which patients with Addison's disease appear to be very susceptible, the administration of sulfadiazine in conjunction with combined desoxycorticosterone acetate and extract therapy has proved to be very effective (56). Previously infections of this severity invariably precipitated an adrenal crisis and if not fatal, were followed by a very prolonged period of convalescence.

By carefully preparing patients beforehand it has also been possible to perform successfully four rather serious operative procedures, viz.: nephrectomy, appendectomy, tonsillectomy and epididymectomy. The remarkably good condition of the patients during the operations and the normal period of convalescence were noteworthy (39).

THE USE OF DESOXYCORTICOSTERONE ACETATE IN THE TREATMENT OF
CONDITIONS OTHER THAN ADDISON'S DISEASE OR CHRONIC
ADRENAL INSUFFICIENCY

Shock. A number of experiments have been conducted by several investigators in an effort to determine whether or not desoxycorticosterone acetate treatment is of benefit either in the prevention or treatment of shock. Fine, et al. (57) noted that treatment with the synthetic hormone greatly reduced the loss in plasma volume which follows intestinal obstruction. Perla (58) has described the effectiveness of desoxycorticosterone acetate in the prevention and treatment of histamine shock in rats and mice and has suggested a plan for treating patients preoperatively in an attempt to reduce the incidence of surgical shock. Wilson and Stewart (59) state that the blood changes which occur after burning injuries are similar to those of adrenal insufficiency, i.e. a reduction in serum sodium and chloride, and a rise in serum potassium and blood non-protein nitrogen. Desoxycorticosterone acetate therapy rapidly restored the sodium and chloride levels to normal and corrected the dehydration and abnormal blood level of non-protein nitrogen and serum potassium. These investigators suggest that the circulatory failure of secondary shock in burns is not due primarily to a low level of serum sodium or to any other blood changes and hence desoxycorticosterone is much less effective in improving circulatory efficiency during secondary shock.

Swingle and his collaborators (60) have investigated the effect of priming doses of desoxycorticosterone acetate in preventing circulatory failure and shock which was induced in dogs by:

- (a) intraperitoneal injections of glucose.
- (b) injections of epinephrin.
- (c) muscle trauma.
- (d) intestinal stripping.

It appeared that desoxycorticosterone acetate treatment successfully protected adrenalectomized dogs against circulatory collapse and shock following the intraperitoneal injection of isotonic glucose solution, following the injection of large amounts of epinephrin, and following trauma to muscle masses. Desoxycorticosterone acetate therapy did not protect these animals against the shock which followed intestinal stripping. The ineffectiveness of desoxycorticosterone acetate therapy in preventing shock after intestinal manipulation was also noted by Selye and his co-workers (61) in intact rats, and by Weil and his associates (62) in normal

rabbits. All three investigators observed that treatment with whole adrenal cortical extract or corticosterone did protect animals subjected to this stress.

Ragan, Ferrebee and Fish (63) have reported that the administration of desoxycorticosterone acetate three to four hours prior to operation prevented a decrease in plasma volume in a group of patients on whom urologic operations were performed with ether anesthesia whereas in control patients a decrease of 3 to 8 per cent in plasma volume was noted.

Orthostatic hypotension. Because of its blood pressure-raising potentiality, desoxycorticosterone acetate was tried as an adjunct in the treatment of a patient with syncopal attacks initiated by orthostatic hypotension. In this patient, continued treatment with the synthetic hormone resulted in an appreciable rise in both systolic and diastolic blood pressure levels and in a definite amelioration of the syncopal attacks, although a pronounced drop in blood pressure still occurred on assuming the upright position. It appeared that the levels of blood pressure had been elevated to a point which was now adequate to prevent syncope although the fundamental abnormality persisted. Engel (64) has also observed the same phenomenon following desoxycorticosterone acetate therapy in a patient with orthostatic hypotension.

Dehydration. Desoxycorticosterone acetate therapy may prove to be extremely useful in maintaining optimum hydration during the course of diseases which normally are associated with a considerable degree of dehydration. It is apparent, however, that little may be expected from hormone therapy unless renal tubular epithelium is intact.

CONCLUSIONS

The synthesis of desoxycorticosterone acetate marks a great advance in our knowledge and understanding of the function of the adrenal cortex. To date, however, little is known concerning the intermediate metabolism of this compound although a number of its physiological properties have been investigated. It appears that regulation of the renal excretion of sodium, chloride and potassium represents one of its chief actions in the body. Desoxycorticosterone acetate does not possess the carbohydrate-regulating potency of whole adrenal cortical extract. The stability of the synthetic hormone, the uniform potency of the preparation and its relative inexpensiveness have been important factors in its widespread use in the treatment of Addison's disease. The marked potency of the preparation requires that care be employed in its use if undesirable and even serious complications are to be avoided.

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SOME CLINICAL OBSERVATIONS UPON THE METABOLISM AND UTILIZATION OF PROGESTERONE; THEIR APPLICATIONS TO GYNECIC PRACTICE¹

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Seven years have passed since the synthesis of progesterone from stigmasterol (1) and from pregnandiol (2). During this time, however, clinicians have been unable to amass sufficient critical therapeutic data to cause the Council on Pharmacy and Chemistry of the American Medical Association to accept progesterone for inclusion in New and Nonofficial Remedies (3). Two sets of circumstances had seemed to portend a more auspicious acceptance of this steroid: 1) the often expressed and generally accepted belief that many gynecologic and obstetric difficulties could be circumvented if a potent corpus luteum principle were available and 2) the stated consensus of workers upon experimental animals that progesterone acted similarly in all respects to active extracts of the corpus luteum. The purpose of this communication is to review some of the attempts which have been made to evaluate the therapeutic rôle of progesterone.

Corner (4) in 1935 made these statements with reference to the clinical possibilities of progesterone: "Here then is a definite hormone, about to be handed to the medical profession to take the place of the meaningless corpus luteum preparations of the past. It has the property of bringing about premenstrual changes and uterine conditions of early pregnancy. What is to be done with it? . . . If there are, among the cases of sterility and habitual abortion, any which are specifically due to uterine disturbances caused by deficiency of corpus luteum, progestin will help them, for it maintains pregnancy in castrated pregnant animals. . . . Progestin might be useful, therefore, in menorrhagia when (if ever) it is due to overaction of estrogenic substance. . . . Reports of cases of threatened abortion treated with progestin frequently refer to the relief of pain as one of the striking results. This is probably due to relaxation of the uterine muscle and, therefore, it is possible that some cases of dysmenorrhea might be benefited by small doses of progestin."

Corner and Allen (5) upon the basis of observations by them and their group (6) drew the following conclusions regarding the identity of progesterone and the active substance of the corpus luteum: "It may be stated that all four of the definitely established effects of corpus luteum extracts upon the uterus; namely, progestational proliferation of the endo-

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metrium, inhibition of the action of pituitrin upon the myometrium, inhibition of uterine motility *in vivo*, and the suppression of menstruation have now been achieved with crystalline progesterone."

Studies of Progestin Deficiency Produced by Surgery. Clinical opinion has frequently predicated the existence of relative or absolute corpus luteum deficiency to explain certain instances of functional irregularities of uterine bleeding, dysmenorrhea, cyclomastopathy, premenstrual tension and edema and recurrent abortion. The establishment beyond peradventure of a corpus luteum deficiency is difficult in clinical practice except in those women who have had bilateral oophorectomy and here, in the non-pregnant women, the effects of estrogenic deficiency overshadow those of progestin deficiency. The bleeding which commonly follows handling of or removal of a corpus luteum occurs before any other effects of progesterone deficiency (i.e., endometrial alterations) can be adequately studied (7, 8) nor can the cause of this bleeding be denied as being due to estrogenic withdrawal. Wiesbader, Engle and Smith (9) were able to prevent the onset of this bleeding by giving intramuscularly 5 mg. of progesterone daily, whereas Morgan and Davidson (8) failed to produce any alterations in the time of this bleeding although they began therapy with progesterone prior to surgery.

The clinical duplication of the specific endometriotropic responses produced by progesterone in castrated experimental animals has not been uniformly successful. Clauberg (10) and Kaufmann (11) reported in 1932 and 1933, respectively, the production of progestational endometria in human castrates by the employment of estrogens and extracts containing progestin. Elden (12), however, repeated these studies in 1936, employing similar therapeutic schedules and using both potent corpus luteum extracts and crystalline progesterone. He was unable to produce any progestational alterations in the endometria of five castrates. Hamblen (13) had reported in 1936 that he had found difficulty in securing progestational responses in young patients with estrogenic bleeding from dosages of progestin similar to those used by Clauberg and Kaufmann.

In considering the pregnant woman, the unequivocal data secured from experimental animals regarding the absolute necessity of the presence of functional corpora lutea for continuation of pregnancy are not available. Pratt (7) reported the cases of two patients from whom corpora lutea had been removed during the first month of pregnancy, even prior to missed menstrual flowings, and in whom no interference with pregnancy or subsequent lactation occurred. Ask-Upmark (14) in 1926 was able to collect and review fifty-one instances of women from whom corpora lutea were removed during the first two months of pregnancy. In nine of these pregnancies continued, despite the fact that in four of them the operations had been performed during the first month of pregnancy. In three of these latter patients both ovaries had been removed. The explanation

which has been advanced to explain these data is that a duality of origin of progesterone occurs in pregnancy: both the corpus luteum and the chorio-placental system perform this function; in instances wherein oophorectomy or ablation of the corpus luteum of pregnancy fails to upset the course of pregnancy, it is assumed that the progesterone formed by the chorio-placental system was ample in amount to protect the uterus against premature expulsion of its contents.

Clinical Methods for Studying Corpus Luteum Activity. The proper assessment of progesterone therapy demands methods which permit the diagnosis of normal and deficient levels of corpus luteum function. As a common occurrence in gynecology, the clinician has found that the possession alone of an active hormone failed to solve knotty therapeutic problems. He found himself handicapped by his inability to diagnose levels of functional activity and, thereby, to delineate properly indications for therapy or to gauge effectively responses to various dosage levels. As yet, no simple, reliable clinical methods exist which afford the critical data desirable for these purposes. The majority of clinical reports has dealt with one or more of the following studies: 1) investigations of uterine contractility; 2) observations upon the effects of progesterone on bleeding; 3) endometrial studies; 4) hormonal titrations of body fluids; and 5) empiric applications of progesterone to presumed corpus luteum deficiencies. Some of the results of these studies will be reviewed. (The last class of data which deals with the reporting of empiric therapy is not considered in this study.)

INVESTIGATIONS OF UTERINE CONTRACTILITY

These studies have direct bearing on the therapeutic employment of progesterone in dysmenorrhea and recurrent abortion.

The intrinsic rhythmic contractility of the uterus is independent of any central nervous control. It has been related to the action of pituitary oxytocin, augmented by the estrogens and suppressed by progestin.

Two methods of studying myometrial activity in the human have been used. The contractions of suitably prepared fresh strips of uterine muscle obtained at laparotomy have been recorded by kymographic tracings and alterations in contractions from the direct action of various principles have been observed. Contractions of the intact uterus have been recorded by inserting a small rubber balloon into the uterine cavity. The balloon is inflated and is connected with a tambour and kymograph.

Knaus (15) in 1934, employing the second method, reported that uterine contractions ceased promptly with ovulation. He attributed this to an effect of progestin elaborated by the corpus luteum. During the gestational phase of the cycle he found the uterus to be refractive to injections of oxytocic principles of the posterior lobe of the pituitary.

Kurzrok and his group (16), however, were unable to confirm Knaus'

observations. They concluded from their studies that the uterus contracted spontaneously during all phases of the cycle; that injections of oxytocins augmented contractions at any time of the cycle; that injections of progestin apparently at times amplified uterine contractility rather than suppressed it; that the administration of progestin during the estrogenic phase of the cycle produced subjective cramping; and that these "cramps" were not associated with any alterations in the character of the recorded uterine contractions. Hamblen and his associates (17), in patients who were receiving cyclic administration of large doses (20 mg.) of progesterone daily for seven to fourteen days for menometrorrhagia, observed that the patients commonly complained of uterine cramping during the course of therapy.

Falls, Lackner and Krohn (18), using injections of only one Clauberg unit of progesterone, were able to quiet the contractions of the uterus during the early puerperium and to prevent uterine contractions normally provoked from 1 cc. of pituitrin. Lubin, Clarke and Reynolds (19), although observing prompt relief of "after pains" from injections of 1 mg. of progesterone, reported that this relief is not necessarily associated with striking changes in uterine motility, as gauged by kymographic tracings.

No critical clinical studies have established the fact that patients with dysmenorrhea or those who experience recurrent abortions have uteri with any characteristic errors of myometrial contractilities. Lackner, Krohn and Soskin (20) reported that they were unable to establish the occurrence of any undue uterine contractility in patients with dysmenorrhea.

THE EFFECTS OF PROGESTERONE UPON UTERINE BLEEDING

The bleeding which, according to Morgan and Davidson (8), occurs within an average of 1.3 days after the surgical removal of recent corpora lutea has been regarded by the proponents of the bleeding-postponing effect of progesterone as proof of their thesis, whereas those advocates of the estrogenic deprivation theory of bleeding consider it to be another bit of evidence in support of their contentions.

Hamblen in 1936 (13) called attention to the following effects of injections of progesterone upon bleeding: when given during episodes of bleeding, flowing is not checked and frequently is increased to the point of alarming hemorrhage; when given during non-bleeding phases of patients with menometrorrhagia bleeding is induced. The latter observation was confirmed by Zondek and Rozin (21) who reported the induction of bleeding in patients with secondary amenorrhea and in normal cyclic women during the intermenstruum following injections of progesterone. Similar observations were made by these observers (22) following the oral administration of anhydro-hydroxy-progesterone.

In regard to the theory that progesterone is concerned with the sup-

pression or delaying of menstruation, neither Morgan and Davidson (8) nor Mazer and Israel (23) were able to postpone the onset of flowing by daily injections of progesterone as large as 10 mg. during the progestational phase of the cycle.

Gillman (24), however, has described three varying effects of progesterone when given during the eighth to tenth days of the menstrual cycle of normal women: lengthening of the cycle, the production of intracyclic hemorrhage without postponing the appearance of normal menstrual bleeding and the shortening of the cycle by the precipitation of premature bleeding and the initiation of a completely new cycle. These effects apparently varied with the amounts of progesterone employed which ranged from total doses of 10 mg. to 30 mg.

The different results, reported by Wiesbader, Engle and Smith (9) and by Morgan and Davidson (8) in studies of the effectiveness of injections of progesterone in postponing bleeding which follows corpus luteum excision already have been cited.

ENDOMETRIAL RESPONSES

Studies of endometria have been commonly employed in clinical attempts to evaluate progesterone. The source of the endometrial tissue studied has been, as rule, material secured by biopsy. Many objections have been raised as to the validity of some of the data reported from studies of endometrial biopsies. These concern, for the most part, the limitations imposed by securing small samples of tissue rather than all of the endometrium for study, possible errors in the interpretation of presumed hormonologic effects and doubts as to deductions drawn from baseline studies as to pretreatment levels of ovarian function. Despite these criticisms, I believe that data secured from critical studies of endometrial biopsies have provided and continue to provide our most valuable information upon the therapeutic effects of progesterone.

The different observations reported by some workers upon the endometrial responses of the castrated woman to progesterone have been cited. These studies took into account the necessary one-two synergism between estrogens and progesterone. The difference in the results obtained by various workers may have been caused by insufficient preliminary "priming" of the endometria by estrogens or by an endometrial refractivity to progesterone.

Studies of endometrial specimens secured by biopsy immediately prior to or within the first twelve to eighteen hours of bleeding have indicated that women with functional dysmenorrhea in the vast majority bleed from progestational endometria (25). Wilson and Kurzrok (26) consider a functional corpus luteum necessary for dysmenorrhea. Such a concept of dysmenorrhea, in itself hardly compatible with the therapeutic employment of progesterone, has led to therapy designed to override or inhibit corpus luteum function.

Estrogens have been employed usually for this purpose; they are administered during the estrogenic phase of the cycle. Despite the fact that therapeutic successes have been reported from relatively small doses of these substances, our group (27) has found that intermenstrual dosages of diverse estrogens as great as 15,000 rat units every two days from the sixth to the fourteenth day of the menstrual cycle, failed to produce any significant depression of corpus luteum function. Sturgis and Albright (28) had reported previously that intermenstrual injections of 10,000 rat units of estradiol benzoate every three days for three to fourteen doses, produced depression of corpus luteum function and resulted subsequently in estrogenic bleeding. Few clinicians have employed such high levels of estrogenic therapy as these in the routine treatment of dysmenorrhea.

Testosterone propionate has been used similarly to estrogens by some workers for its supposed corpus luteum inhibiting action. Geist (29) estimated that a total dose of 500 to 900 mg. of testosterone propionate for a single cycle, with therapy started not later than the sixth day, was necessary for complete inhibition of corpus luteum function. Our group (30) showed that the administration of four to five doses of testosterone propionate of 25 mg. each during the first half of the menstrual cycle had no depressing effects on corpus luteum function. Rubinstein and Abarbanel (31), however, obtained excellent relief of dysmenorrhea from individual doses of 5 mg. of testosterone propionate given two or more times prior to flowing.

As early as 1936 Hamblen (13) called attention to the fact that progesterone when given in amounts similar to those employed by Clauberg (10) and Kaufmann (11) commonly failed to produce any significant progestational alterations in the endometria of patients with menometrorrhagia associated with estrogenic endometria. Priming of these endometria with estrogens and the subsequent simultaneous administration of estrogen and progesterone increased the incidence of progestational responses but did not lead to any consistent occurrence of these. Two theories were advanced to explain the observations: an endometrial refractivity to progesterone (32); and an inadequate or inefficient metabolism of progesterone when it was administered intramuscularly in oil solution (33, 34).

On the assumption that endometrial refractivity to progestin supplied intrinsically might be an etiologic factor in certain instances of menometrorrhagia and upon the basis of the established hemostatic-hemorrhagic effects of estrogen and progesterone, a system of cyclic steroid therapy was devised and applied to the treatment of functional menometrorrhagia (32). Recent assessment of this system of therapy in a group of fifty-one women (17) has indicated that repeated series of this form of treatment apparently are able to overcome endometrial refractivity in a large number of patients but not in all. Few patients gave consistently positive responses to this therapy but, as a rule, if responses

were obtained, they followed one or more series of therapy in which no progestational effects occurred. It was found that 45.5 per cent of the patients investigated after the cessation of therapy continued to experience normal ovarian responses (i.e., bled from progestational endometria), whereas prior to therapy they had bled from estrogenic endometria.

We are convinced that an important factor in overcoming the supposed endometrial refractivity in these cases is the administration of estrogens. We cannot be certain at present that administered progesterone exerts any specific effects in this regard. We have encountered some evidence that cyclicly administered estrogens alone may result in progestational responses of the endometria in patients with estrogenic bleeding (27).

Inhoffen and Hohlweg (35) in 1938 described the preparation from estradiol of pregnen-in-on-3-ol-17 (anhydro-hydroxy-progesterone; ethinyl testosterone) which they found to exert progestational effects when given orally to immature mice. Hamblén (36) in May, 1939 reported that this steroid was tolerated well by women and when administered orally produced progestational alterations in their endometria. Salmon, Walter and Geist (37) described the production of progestational alterations in the endometria of post-menopausal women by the oral administration of anhydro-hydroxy-progesterone and Zondek and Rozin (38) reported the induction of intermenstrual bleeding from anhydro-hydroxy-progesterone, intermenstrually and orally administered similarly as they had described for progesterone.

Subsequent reports by our group (39, 40) indicated that cyclic therapy, which embraced the use of orally administered estrogens and anhydro-hydroxy-progesterone, was able to induce progestational alterations in the endometria of patients with estrogenic menometrorrhagia as effectively as intramuscularly administered estrogen and progesterone. No evidence was secured, however, from a group of 36 women, treated by this cyclic oral steroid therapy (40), that any ultimate salvage was effected. It was suggested by us that probably this was due to the fact that smaller doses of estrogens (orally administered) were used than in the injected steroid therapy.

No other steroids, other than progesterone and anhydro-hydroxy-progesterone, have been reported capable of producing progestational alterations in the endometrium of women. Desoxycorticosterone acetate, despite its progesterone-like properties in experimental animals, has not been found capable of inducing progestational responses in women (41).

STUDIES ON HORMONAL TITERS ON BODY FLUIDS

Investigations of hormonal levels would appear to be a logical approach to the clinical evaluation of progesterone therapy. Theoretically such studies should permit obtaining the following pertinent data: 1) the establishment of the diagnosis of corpus luteum failure and the grading of

its severity; 2) the estimation of the therapeutic requirements of progesterone necessary to complement the deficit established, and 3) proof of the efficiency of the metabolism and utilization of the progesterone given.

The problem has been rendered difficult by the fact that biologically active progestin can be found in human tissues and fluids only in small quantities when the Corner-Allen technic of assay is used. Adler and his co-workers (42) and Ehrhardt (43) could detect but small amounts in placentas and urines of pregnant women. Clauberg and his associates (44) obtained a questionable progestational reaction with an extract prepared from approximately 50 gm. of human corpora lutea. Pratt and his group (45), however, were able to get positive tests in the immature rabbit with extracts equivalent to 60 gm. of corpora lutea. Loewe and Voss (46) found only one rabbit unit of progestin in 20 liters of urine collected from women during the last five days of the progestational phase of the cycle. Our group (47,48) showed that two young women receiving 20 mg. of progesterone intramuscularly daily excreted in their urines no biologically active progestin, as judged by the Corner-Allen technic, and that a young woman receiving 40 mg. of anhydro-hydroxy-progesterone daily by mouth likewise failed to excrete any biologically active progestational substances. More sensitive methods for the bioassay of progestin have been described in recent years: a method based upon the property of progestin to inhibit the vaginal effects of estrogens (49); one which utilizes the fact that progestin produces an increase in the size of the ovipositor of the bitterling (50); and a method which employs the intrauterine application of progestin (51, 52). These methods, while permitting the qualitative recognition of small quantities of progestin in body tissues and fluids, have not been applied, as yet, to general clinical studies such as those which concern us at present.

The work of Venning and her associates (53) in Montreal has provided a gravimetric method for the quantitation of sodium pregnandiol glucuronide in the urine and these workers have submitted evidence that this steroid-complex represents a major metabolic product of progestin. During the past three years a relatively large number of studies upon pregnandiol studies has appeared. These studies, in general, have tended to point out failings and shortcomings of the Venning technic and to cast doubt upon its usefulness as a clinical method for evaluating corpus luteum function or for gauging the level of required progesterone therapy.

Simultaneously Stover and Pratt (54) and our group (55) differed with one of the primary observations of the Montreal group by which they related pregnandiol titers and progestin metabolism: these two groups were able to recover little or no pregnandiol following injections of progesterone into women not spontaneously excreting this compound, whereas Venning and her group had reported recoveries under similar conditions of amounts of pregnandiol comparable to yields of 12 per cent to 46 per cent of that

expected from the amount of progesterone given. The subsequent studies of our group have not altered materially our point of view in this matter.

Our group (34), however, reported that the recovery of pregnandiol following injections of progesterone to women with estrogenic bleeding was improved by endometrial priming with estrogens and the concomitant administration of estrogens and progesterone. The Montreal group in their report of 1940 confirmed these observations. We found, furthermore, that, in the treatment of estrogenic bleeding, the best yield of pregnandiol followed estrogenic 'priming' and the concurrent administration of estrogens, progesterone and chorionic gonadotropin. This result was related by us to the production of a hormonal synergism similar to that which exists in the normal woman during the progestational phase of the cycle: The 1940 report of the Montreal group also confirmed indirectly this observation: they obtained their best yields of pregnandiol when progesterone was given to normal women during the progestational phase of the cycle.

Our group (55) made observations which were somewhat similar to those of the Montreal group in regard the role of the endometrium in the metabolism of progestin into pregnandiol. These workers had reported their inability to recover pregnandiol following injections of progesterone to hysterectomized women. We reported that the urinary excretion of pregnandiol was impaired apparently by hysterectomies done upon two women during the progestational phases of their menstrual cycles. In these two patients the presence of functional corpora lutea was verified at operation. We reported, likewise, that curettages done during the progestational phases of menstrual cycles of three women interfered with their urinary outputs of pregnandiol. The Montreal group in 1940 continued to believe that a functionally adequate endometrium facilitates the metabolism of progesterone but reported that, by using larger doses of progesterone than those used formerly by them, they had been able to recover small amounts of sodium pregnandiol glucuronide from the urines of hysterectomized women.

Buxton and Westphal (56), however, had shown previously that the endometrium was not necessary for the conversion of progesterone into pregnandiol since injections of progesterone into the male were followed by the urinary excretion of pregnandiol. Our group (57) also had made similar observations and had reported that the male apparently metabolized progesterone in this regard better than woman.

Our studies on the male, furthermore, indicated that pregnandiol is not a specific metabolic product of progesterone alone. We (58) were able to recover sodium pregnandiol glucuronide from the urine of a male during two series of therapy with desoxycorticosterone acetate; one comprising 5 mg. daily for five days, the other 10 mg. a day for five days. Similar therapy in the female (41), however, did not result in the urinary elimina-

tion of any pregnandiol which was attributable to the desoxycorticosterone acetage given.

Our observations, moreover, have failed to confirm the contention of the Montreal group that pregnandiol is excreted uniformly during the progestational phase of the cycle. These workers found a definite and constant relationship between *Mittelschmerz* and the initial appearance of pregnandiol in the urine and described its excretion as continuous from that time until just prior to the onset of menstrual bleeding. We have found that, as a rule, pregnandiol does appear in the urine about the supposed time of ovulation but that its excretion curve is most irregular and that patients may excrete no pregnandiol for two or three consecutive days during the progestational phase of the cycle. While the Montreal group commented upon the marked variations in the total amount of pregnandiol excreted by healthy cyclic women, they placed the average cyclic excretion of pregnandiol at 45 to 55 mg. Our observations have pointed to the lack of any absolute consistencies in correlations between the level of pregnandiol output and the nature of the endometria associated with bleeding.

The following observations were made in this regard upon a group of twenty-four young healthy women who had cyclic bleeding from progestational endometria:

Six of these women excreted *no* pregnandiol during cycles which were concluded by bleeding from progestational endometria (biopsies done at the onset of bleeding); in three patients the endometria were diagnosed as normal progestational; in three patients as mixed progestational.

Three other women with progestational bleeding excreted total amounts of sodium pregnandiol glucuronide of 7 mg. or less for the cycle.

The amounts of sodium pregnandiol glucuronide excreted during cycles which terminated in bleeding from normal progestational endometria ranged from 0 to 99 mg.

The amount of sodium pregnandiol glucuronide excreted during cycles which terminated in bleeding from poorly differentiated or mixed progestational endometria varied from 0 to 173 mg.

The time of the initial appearance of pregnandiol in the urine varied from the fifth to the twenty-second day of the cycle. The time of disappearance of pregnandiol from the urine varied from 72 hours prior to bleeding to the end of the first day of bleeding.

Likewise, when patients with functional irregularities of uterine bleeding were investigated as regards their endometrial-pregnandiol correlations, similar inconsistencies were observed:

Patients with menometrorrhagia associated with bleeding from estrogenic endometria excreted amounts of sodium pregnandiol glucuronide during their non-bleeding phases which varied from 0 to 49 mg.

Patients with menometrorrhagia associated with bleeding from progestational endometria excreted amounts of sodium pregnandiol glucuronide during their non-bleeding phases which varied from 0 to 135 mg.

Similar inconsistencies were observed in the investigation of endometrial-pregnandiol correlates of patients with functional dysmenorrhea.

Two patients with functional dysmenorrhea associated with estrogenic bleeding excreted during their intervals 0 and 29 mg. of sodium pregnandiol glucuronide respectively.

Three patients with functional dysmenorrhea associated with progestational bleeding excreted amounts of sodium pregnandiol glucuronide during their non-bleeding intervals which varied from 16 to 51 mg.

Wilson, Randall and Osterberg (59), however, found closer relationships between pregnandiol excretion and endometrial proliferation and stated that an abnormal microscopic appearance of the progestational endometrium was nearly always associated with low urinary values of pregnandiol. Hain and Robertson (60), while making somewhat similar observations, reported a patient who excreted 10.5 mg. of pregnandiol during a cycle which terminated with estrogenic bleeding. A recent editorial in the *British Medical Journal* (61) sums up the matter as follows: "At first it was thought that a quantitative estimation of the excretion of pregnandiol during the menstrual cycle might constitute a test for corpus luteum function. Attempts to establish normality have, however, revealed such a wide range in total excretion that quantitative differences do not appear to have any pathological significance."

Cyclomastopathy, i.e., mastodynia, Schimmelbusch disease and cystic mastitis, has been related commonly to disturbed ovarian function (25). In 1937, Lewis and Geschickter (62) described gratifying clinical responses in cystic disease from estrogenic therapy combined in some instances with injections of the lactogenic principle of the pituitary. Recently Bucher and Geschickter (63) have investigated the hormonal levels of patients with cyclomastopathy; they described estrogenic titers as being in general normal, but they found the pregnandiol output of patients with mastodynia or with adenosis to be lower than average normal values. Upon the basis of these findings Geschickter (64) has administered progesterone in doses of 5 mg. twice weekly during the last two weeks of the menstrual cycle with beneficial results.

Despite the fact the gynecologists and obstetricians for years have assumed that one of the causes of recurrent abortions was intercurrent ovarian (corpus luteum) failure and despite the clinical enthusiasm which exists in some circles (65 to 67) over therapeutic results obtained with small doses of progesterone in preventing abortion, little objective evidence exists that corpus luteum deficiency is the primary cause of recurrent abortion.

The Montreal group expressed the hope that their method for estimating pregnandiol titers would permit direct measurement of the progesterone deficit under these circumstances and, thereby, permit the administration of adequate therapy. They have reported successful employment of therapy gauged by pregnandiol titers.

Stover and Pratt (54), however, failed to find low pregnandiol titers in women with histories of previous recurrent abortion or in those threatening to abort. Buxton (68) in general made similar observations but described several women, who did excrete very low pregnandiol titers. These women aborted despite intensive therapy with progesterone. In no instance did the therapy produce any elevation of the pregnandiol titers.

Hamblen (69) has made observations similar to those of Buxton. He observed that in patients with low pregnandiol titers daily doses of progesterone as large as 20 mg., complemented or synergized with estrogens, failed to prevent abortion or to increase the pregnandiol output. One patient excreted no pregnandiol for ten days prior to abortion, despite the fact that she was receiving therapeutically 10 mg. of progesterone a day. Hamblen also reported that no absolute relationship existed between the occurrence of abortion and the titers for urinary pregnandiol. One patient with values for pregnandiol well in the higher bracket of normal threatened to abort for nearly a month. During this time, despite uterine cramping and bleeding, she continued to excrete normal amounts of pregnandiol. This patient subsequently was delivered at term.

Cope (70) believes that the complete absence of pregnandiol from the urine in pregnancy is always evidence of a serious abnormality. He is of the opinion that such a finding in early pregnancy indicates that abortion will occur. The absence of pregnandiol in the urine in late pregnancy is considered by him to be evidence of death of *fetus in utero*. The editorial comment of the British Medical Journal (61) upon Cope's report emphasizes that a study of pregnandiol titers cannot be regarded a reliable method of diagnosing fetal death "as in only a small percentage of cases of fetal death can the absence of pregnandiol be demonstrated, and in others it is normal. Such a test can only be used as an adjuvant to other methods of investigation."

These observations by various workers who have studied urinary pregnandiol titers, therefore, show rather striking degrees of disagreement. It is obvious from this review that Venning's technic, instead of implementing studies of corpus luteum physiology and pathology, has only added to the quagmire of uncertainty. There are several explanations which may be suggested for our present confusion:

- 1) Proof that the dried powder, recovered by Venning's technic, and weighed under the assumption that it is sodium pregnandiol glucuronide, is actually and undeniably this chemical compound is usually lacking. To subject each precipitate obtained to chemical analysis would be an impossible task if a broad program of clinical investigation is underway. Smaller precipitates may not even permit satisfactory melting point determinations. Hydrolysis to free pregnandiol, recrystallization and reweighing add more certain data but decrease the flexibility of the method; the same is true of estimations of the glucuronide fraction. Many of the

precipitates reported upon are accepted as sodium pregnandiol glucuronide on little more than faith in the specificity of the extraction method.

2) Assuming, however, that no uncertainty may exist as the chemical identity of the precipitates obtained by Venning's technic, no clear-cut proof has been submitted that pregnandiol is necessarily the major product of progestin metabolism. It may be that qualitative fluctuations in this metabolism may be more important than quantitative variations in pregnandiol titers. In addition to free pregnandiol and sodium pregnandiol glucuronide, Marker and his group (71 to 75) have found other members of the pregnane-group in the urine of normal and pregnant women: pregnanol-3(α)-one-20, "epipregnanolone"; allo-pregnandiol-3(α)-one-20, 'epi-allo-pregnanolone; allo-pregnandiol-3(α),20(α); and allo-pregnandiol-3(β),20(α). The third one of these compounds has a melting point close to pregnandiol and as much as 7 mg. of it have been found in a liter of pregnancy urine. Westphal (76) calling attention to the preceding studies cautions that pregnandiol should not be regarded as the only compound with 21 carbon atoms which results from the reduction of progesterone.

At this point of the discussion, it may not be completely irrelevant to observe that it seems strange that the monkey which has been so faithful in supplying scientific data on reproductive physiology and sex endocrinology excretes no pregnandiol (77, 78).

The studies of our group have comprised the quantitation of well over 6,000 specimens of urine for pregnandiol titers. We have at all times followed, without any modifications, Venning's technic. Close adherence to her method has been facilitated by having had a research associate common to both groups (C.J.P., 17, 39-41, (79)). We have made one modification in the manner of reporting results: from the beginning we have reported our results as mg. of sodium pregnandiol glucuronide rather than as mg. of pregnandiol, as the Montreal group has done.

SUMMARY AND CONCLUSIONS

This survey has presented ample evidence that the therapeutic rôle of progesterone is yet to be delineated clearly. Clinical studies by various groups have yielded data which are often contradictory and irreconcilable. No method of approach has afforded conclusive and unchallenged facts regarding the physiology and pathology of the corpus luteum or the therapeutic applications of progesterone. Despite its adverse critics, the method of endometrial biopsy has yielded, perhaps, the least conflicting data of all of the various studies.

In view of these facts, any summary or conclusions at the present time must be based upon opinions of an individual or of a single group rather than upon a consensus, since no one worker finds all his data unchallenged. Our views at this stage may be briefly recapitulated:

The quieting action of progesterone upon uterine muscle has not been

established. Any predication of therapy, as in habitual abortion and dysmenorrhea, upon this assumption is founded upon theory and not established fact. On the other hand, there is some reason to believe that injections of progesterone produce subjective "cramps" if not actual uterine contractions. Likewise it cannot be held as proven that progesterone is a biologic antidote to posterior pituitary oxytocin. Instead of suppressing or delaying menstruation, injections of progesterone apparently induce bleeding if given during the intermenstruum and increase the duration and severity of bleeding if given during episodes of flowing. Therefore, of the "4 definitely established effects of corpus luteum extracts" upon the uteri of experimental animals cited by Corner and Allen (5), only the endometrial effects of progesterone have been established for woman. Therefore, again in the question raised by Corner (4) in 1935 regarding progesterone "what is to be done with it?" must be considered.

Clinical studies have not related etiologically corpus luteum failure or deficiency with recurrent abortion or dysmenorrhea. Likewise clinical studies of the pharmacology of progesterone have established no clear-cut specific indications for the therapeutic use of this steroid in these conditions.

There is a mass of clinical data (80, 81), however, which associates a large majority of functional uterine bleeding (menometrorrhagia, amenorrhea, etc.) with a failure of occurrence of ovulation and an absence of corpus luteum activity. Despite this fact, therapy with an agent capable of inducing interval bleeding and of producing progestational effects upon endometria previously primed with estrogens, seems to offer *per se* nothing more than supplemental or substitutional treatment. Evidence has been submitted that an endometrial refractivity to progesterone may account for some instances of functional bleeding and that the cyclic administration of estrogen and progesterone under these circumstances may effect complete therapeutic salvage. As yet, no absolute proof has been submitted that progesterone constitutes an essential part of such a therapeutic schedule.

No phase of the recent corpus luteum studies has proven more disappointing than that which has been concerned with the gravimetric determination of urinary sodium pregnandiol glucuronide. The near future may furnish a sadly needed accurate measuring stick for corpus luteum function; until that time we shall continue probably to find ourselves in our present awkward predicament of possessing an active corpus luteum hormone and yet of being unable to establish a clear-cut indication for its therapeutic employment.

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PAINFUL LESIONS OF THE FEET

THEIR BASIC PATHOLOGY AND TREATMENT

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Lack of knowledge of the basic pathology underlying many of the common painful ailments of the feet leads to prolonged ineffective treatment, often repeated at intervals throughout the patient's life. Patients accept, without complaint, the necessity of returning to a chiropodist at intervals of five or six weeks to obtain relief from an easily remediable foot lesion.

The basic pathology is a compression of the soft parts, the skin and subcutaneous tissue between an underlying bony prominence and the leather of the shoe or another opposing bony prominence. The response to this compression is a thickening or cornification of the skin, the formation of a bursa at the compression point, and eventually cartilaginous and later bony proliferation of the bone at the compression point. This produces a vicious circle and eventually causes symptoms severe enough to force the sufferer to consult an orthopedic surgeon for permanent relief. Relief can be obtained only by relieving the compression. If this cannot be brought about by well-fitting footwear or shoe corrections, arches or other devices, the underlying bony protuberance should be removed.

Common corn: This usually occurs on the fifth toe over the proximal interphalangeal joint and is caused by the pressure of a small exostosis of bone or cartilage underlying the thickened skin and compressing the soft parts against the shoe. Repeated removal of the hardened, thickened skin will be of no value beyond temporary relief until the thickening recurs. Removal of the underlying exostosis will give permanent relief. The thickened skin will slough off in a few weeks and there will be no recurrence.

The soft corn: The soft corn is similarly cornified skin that occurs because of pressure of the phalanx of the fifth toe against a projecting portion of the phalanx of the fourth toe. The condition is usually started by a tight or ill-fitting shoe which causes a slight periosteal irritation followed by a slight proliferation of the bony prominence. This is enough to start a vicious circle of increasing pressure. Soft corns have a soft, macerated appearance because they occur where the skin is moist and there often is a superimposed ringworm infection. The indication is to remove the offending bony protuberance through a small incision under local anesthesia. After the offending pressure has been removed, the cornified skin will slough off and not recur. Patients are often treated for months and years by capable dermatologists who employ ointments, x-rays and minor surgical procedures without success.

¹Deceased November 2, 1941.

Hallux valgus: The painful and often ulcerating bursa over the mesial aspect of the great toe is due to similar pressure of the shoe against the metatarsal head. The situation here is complicated by the bowstring effect of the short toe flexors and adductors. In addition to removing the exostosis, steps must be taken to prevent a recurrence of the valgus deformity of the great toe. In my opinion, the most effective procedure is hemi-phalangectomy.

Tailor's bunion: "Tailor's bunion" is a picturesquely named bony protuberance at the distal end of the fifth metatarsal. The name "tailor's bunion" is used because tailors traditionally sit crosslegged at their work, resting their feet on the lateral aspect, supposedly at the usual site of the fifth metatarsal protuberance. Normally, there is a small tuberosity at the lateral aspect of the fifth metatarsal head and irritation of this tuberosity produces the exostosis that causes a tailor's bunion. If the symptoms are sufficiently annoying, resection of the protuberance will readily cure all symptoms.

Dorsal bunion: Due to the modern practice of lacing shoes tightly, there is often irritation of the margins of the joint between the internal cuneiform bone and the first metatarsal with the resulting production of marginal exostoses, often with an overlying bursae and reddened, cornified skin. If relief is not obtained by felt padding on the tongue of the shoe or by strap shoes that do not exert pressure on the painful point, resection of the exostosis is indicated. Since the condition is really a traumatic arthritis of the joint between the internal cuneiform and the first metatarsal, many orthopedic surgeons advise operative fusion of that joint.

Hammer toes: Hammer toes in themselves are not painful but the corns that form at their apex are often extremely tender. Occasionally painful callouses form at the distal end of the hammer toe where it rests against the sole of the shoe. Operative correction of the hammer toe, if properly performed, promptly cures all symptoms.

Metatarsal pain: Pain beneath the heads of the metatarsals occurs chiefly in women who, because of high heels, bear a large portion of their weight on the metatarsal heads. The soft parts are compressed between the metatarsal heads and the sole of the shoe with resulting pain. Often, small bursae form beneath the metatarsal heads. Metatarsal pads or bars designed to support the weight behind the metatarsal heads, combined with lower-heeled shoes, usually afford relief. A sub-variety of metatarsalgia often causes severe lancinating pain usually along the fourth toe. Since Morton (1) described it in 1875, it has been known as "Morton's metatarsalgia." Most observers believe that it is caused by pressure of the fourth metatarsal upon the digital nerve. It can often be relieved by well-fitted metatarsal supports but occasionally a case will prove recalcitrant to all conservative measures. Resection of the digital nerves to the fourth toe and resection of the metatarsal head will result in a cure.

Sesmoid bones: Occasionally, a painful callous forms beneath the mesial or lateral sesmoid of the big toe. Often such callouses are mistakenly treated as papillomata, by resection, applications of acid and coagulation. The only curative procedure is to relieve pressure at this point. If pads and corrective shoe devices are unsuccessful, resection of the offending sesmoid is indicated and will bring about a rapid cure.

Accessory or prominent scaphoids: Occasionally, there is a large accessory scaphoid mesial to the scaphoid bone. The soft parts are compressed between the side of the shoe and the accessory scaphoid. Resection of the offending bone will produce a prompt cure. Occasionally even though there is no accessory scaphoid, an unusually large and prominent scaphoid can produce similar symptoms. Resection of the projecting portion is indicated.

Accessory fifth metatarsal epiphysis: Rarely, an accessory epiphysis at the proximal end of the fifth metatarsal will cause symptoms sufficient to indicate its resection.

Painful heels: One of the most stubborn, resistant conditions that orthopedists are confronted with is the painful heel. Only a small percentage of painful heels show x-ray evidence of spur formation at the painful point. A great majority of x-rays are negative. The pain is caused by compression of the soft parts between the os calcis and the heel of the shoe and usually occurs in individuals who are on their feet many hours a day. An infectious element may be a factor in producing the symptoms but in my opinion this is extremely rare. I think the etiology is chiefly mechanical. Not so many years ago, most painful heels were considered to be due to a previous attack of gonorrhea, but there is no evidence to substantiate this theory. Treatment should be designed to relieve pressure from the os calcis by means of special plates and shoe corrections. Occasionally, relief can be hastened by repeated injections of novocaine into the painful area. Operative intervention is to be avoided as the results after operation are extremely unsatisfactory.

Painful posterior bursitis of the heel: Another variety of painful heel, less common than the preceding, is posterior bursitis of the os calcis. The bursa that lies posterior to the insertion of the tendo achilles is pressed between the os calcis and the shoe. Usually, poorly fitting shoes start the vicious circle. Due to irritation, increased bone proliferation occurs and the pressure becomes more marked even with well-fitting shoes. Surgical removal of the bursa is usually followed by a recurrence. A plastic operation on the heel, such as the procedure devised by Zadek (2), will effectively cure the condition.

In addition to the specific syndromes enumerated above, miscellaneous callous areas may develop on normal or abnormal feet due to deviations in gait or structure. Callous at the mesial aspect of the great toe and beneath the fifth metatarsal head are the most frequent locations. Attempts should

be made to relieve the pressure by shoe corrections if necessary, and if unsuccessful, the local pathology should be carefully studied and surgical means devised to remove the underlying bony projection.

Painful lesions of the feet should not be casually treated by the surgeon or orthopedist. They cause symptoms out of all proportion to their size and seeming importance.

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ASEPTIC INFARCTION OF THE KIDNEY¹

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This lesion is of interest to the clinician because it is most often a complication of chronic rheumatic cardiovalvular disease. Any cardiac lesion associated with arrhythmia, such as auricular fibrillation, may be the source of emboli to the kidneys with resulting infarction. In addition to rheumatic disease, arrhythmia may be associated with arteriosclerotic and thyrotoxic heart disease. Mural thrombi from myocardial infarction due to coronary thrombosis may also lead to embolization. In bacterial endocarditis the emboli usually contain bacteria and, therefore, these lesions are outside the scope of this communication. To the surgeon, acute infarction of the kidney may afford a diagnostic problem. It may simulate acute surgical lesions such as intestinal obstruction, acute cholecystitis or appendicitis, and peritonitis resulting from perforation of a viscus, or an acute renal colic. Occasionally nephrectomy has been performed on an infarcted kidney because of an erroneous clinical diagnosis. Old small infarcts of a kidney may cause pyelographic changes suggesting renal disease such as neoplasm. I have observed one such case.

The case reported here was clinically proved to be a rather extensively infarcted kidney by excretory urogram and cystoscopy, but a subsequent increasing blood pressure suggested that the blood supply was only partially blocked. Incidentally, the increasing tension was followed by heart failure, and the problem arose as to whether nephrectomy was not indicated. However, the patient's general condition precluded any surgery.

CASE REPORT

History. (Adm. 437530). The patient was a 26 year old unmarried salesgirl, who was first seen at home in urological consultation on March 13, 1939 for an acute attack of severe right renal colic associated with a fever of 103.6°F. She was referred to the hospital and admitted to Dr. Baehr's Service two days later. It was learned that at the age of four years she was said to have had "rheumatism." For the previous eight years heart disease was known to have been present following a febrile attack. During this period she had been hospitalized several times at other institutions because of cardiac symptoms consisting of dyspnea, precordial pain, palpitation, and was told that she had an enlarged heart and liver. During the previous year, cough and brown streaked sputum had been present. During the month prior to admission she had abdominal pain, nausea, and vomiting and had been taking digitalis because of irregular cardiac rhythm. Two weeks before admission swelling of the ankles was noted for the first time and muscular pains were present. Acute right loin pain radiating to the right groin commenced four days

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before admission, lasted ten hours, and was not accompanied by hematuria. The family physician found marked loin tenderness.

Examination. She appeared well developed, well nourished and not acutely ill. Her chest was clear to percussion and auscultation. The cardiac sounds were of good quality. There was a long rumbling diastolic murmur at the apex. The pulmonic second sound was accentuated. The rhythm was completely irregular but slow. The blood pressure was 118 systolic and 60 diastolic. Abdominal examination revealed an enlarged slightly tender liver and a non-tender tip of the spleen. There was right costo-vertebral angle tenderness. The rest of the examination was essentially negative. The temperature on admission to the hospital was 100.4°F. and the diagnosis of rheumatic heart disease, congestive failure and right renal infarction was made.

Laboratory Data. The urine examination showed a specific gravity of 1026, a trace of albumin, and an occasional white blood cell. Daily urine examinations for the next two weeks showed the same findings with a very rare red blood cell in the sediment. The sedimentation time was 23 minutes for 18 mm. Blood examination revealed hemoglobin 65 per cent, white blood cells 12,000 with 78 per cent polymorphonuclear leucocytes. The venous pressure was $7\frac{1}{2}$ cm. rising to 13 cm. on right upper quadrant pressure, the saccharine time was 25 seconds. The blood urea nitrogen was 12 mg. per cent, and the total protein was 5.3 mg. per cent. The blood Wassermann reaction was negative. An electrocardiogram revealed an auricular fibrillation with slow ventricular rate, right axis deviation and depressed R-T transitions in leads II and III, with T wave changes attributed to digitalis.

Urological Investigation. Examination of the abdomen by x-ray showed an apparent enlargement of the liver and spleen, but normal sized and shaped kidneys. An excretory urogram showed no visualization of the right upper urinary tract whereas the left appeared to be normal. On cystoscopy, the bladder and ureteral orifices appeared normal. Both ureters were catheterized the full distance to the pelves. There was a prompt flow from the left side with excellent indigocarmine excretion. On the right side, no flow was obtained either spontaneously or after injecting solution. A right ureteropyelogram was then performed. This failed to show any abnormality.

From these findings, namely, non-function by excretory pyelography and cystoscopy with a normal retrograde pyelogram and with the clinical picture of severe acute loin pain in the presence of rheumatic heart disease and auricular fibrillation, the diagnosis of a renal arterial embolization and infarction seemed obvious. The absence of any history or evidence of hematuria or hemoglobinuria was noteworthy.

Course. About two weeks after admission and following an initial improvement the patient began to have dyspnea and orthopnea with tachycardia and moist râles at the bases. The blood pressure was 145 systolic and 90 diastolic. Evidences of slight generalized and sacral edema were noted. Her temperature was 101°F. Several days later, her ventricular rate was 120, while the radial pulse rate was 85 per minute. Cardiac murmurs previously heard were not audible. In addition there were signs of fluid at the right base. Salicylates were administered and given to saturation. Her blood pressure had risen to 170 systolic and 100 diastolic. There was no azotemia, and the urinary concentration seemed adequate. It appeared that in view of the rising blood pressure, renal ischemia due to incomplete blockage of the renal blood supply might be the etiological factor as in the experimental hypertension of Goldblatt (10, 11). Inasmuch as there was increasing heart failure due to the rising vascular tension, the question arose as to whether right nephrectomy might not be indicated. The increased blood pressure persisted but the patient's condition was such that she could not survive a nephrectomy. Hope was expressed that with healing of the infarct, the hypertension might subside. Parenteral digi-

talis medication resulted in a slowing of the cardiac rate; the blood pressure remained elevated. The congestive failure increased in spite of the usual diuretic medication and she died four weeks after admission. Unfortunately no necropsy was obtained.

DISCUSSION

Aseptic infarction of the kidney has only been occasionally discussed in the literature since Traube (1) reported the first proven case. The majority of cases particularly the smaller infarctions are not clinically recognizable because they have no symptoms (2, 3). Hoxie and Coggin (3) found the incidence of all types of infarction to be 1.4 per cent of a total of 14,411 autopsies.

Embolism of the main renal artery or its branches is one of the more common causes of aseptic infarction. The cause of the embolism is most often cardiac disease with auricular fibrillation and usually rheumatic in origin. Other conditions may lead to infarction such as thrombosis of the renal artery brought about by local traumatic or infectious disease. Aseptic emboli may arise from places other than the heart and rarely from peripheral veins in the presence of an open interventricular septum or patent foramen ovale. Idiopathic infarction has occurred, as was recently reported by Sheppard (4), in a young adult. Barney and Mintz (2) found a normal heart in only 6 out of 136 post-mortem examinations whereas in 95 per cent of their cases the heart and its valves showed changes.

The symptoms may vary from none, to sudden severe pain in the abdomen and flank accompanied by nausea, vomiting, fever, and prostration. Temperature may be absent or rise to 103 to 104°F. The physical signs may point to the kidney, with tenderness and rigidity of the loin, costo-vertebral areas and even the upper abdomen anteriorly.

The findings in the urine are of particular interest because contrary to expectation hematuria may be absent. Hoxie and Coggin (3) found that only 30 per cent of 117 cases had hematuria of which 4 had gross hematuria. In fact, the urine may show no changes at all. Albuminuria was the most constant abnormality found by Aschner (5) in his series of 18 cases 2 of which were from this hospital. Other observers (6, 7) have confirmed the frequency of albuminuria. Occasionally, hemoglobinuria may be present and found to be unilateral by cystoscopy (Libman and Fishberg (8)).

In a patient with a source for an embolus and with localizing acute symptoms referable to the kidney, confirmation of the diagnosis of infarction may be helped by urological studies. In the first place, plain roentgenographic studies of the abdomen will show normal outlines of the kidneys with no evidences of calculi. On excretory urogram no visualization will be present in the severer infarctions while poor visualization may result from smaller infarctions. Cystoscopic examination will confirm the excretory urogram. The findings may vary from no function as in this case to diminished or fair function depending on the amount of infarction.

Probably the most interesting feature of this case was the development, about and two one-half weeks after infarction, of increasing blood pressure which may have been contributory to the uncontrollable cardiac failure. Undoubtedly if the patient's condition had warranted the risk, nephrectomy would definitely have been indicated in the presence of her rising and persistent hypertension. Incidentally it was obvious that the rise in blood pressure was not due to an improvement in her cardiac status because the opposite condition was apparent. The association of hypertension with renal infarction is rare. Fishberg (12) observed hypertension developing after typical embolism of the renal artery in a patient who was admitted for myocardial infarction. In the series of Hoxie and Coggin (3) previously mentioned, although 34 per cent of the patients had a blood pressure over 140 systolic and 90 diastolic, in no instance could the rise in blood pressure be proved as due to renal arterial embolization.

Of twenty-one other clinical cases of aseptic infarction observed at this hospital between 1928 and 1940 only two had hypertension. In one case with rheumatic cardiovalvular disease, some elevation of the blood pressure was noted three years after the patient had her infarction. In the other case a temporary hypertension was noted some time after infarction, but several years later, the blood pressure was found to be normal again. We have observed many patients with old infarcts of the kidney at necropsy who did not have hypertension so that, although occasionally hypertension may follow infarction, persistent hypertension cannot be considered a typical sequel to infarction. In this connection, the experimental observation of Cash (9) should be mentioned. He found that where the total kidney mass was reduced by one-half (nephrectomy) ligation of the blood supply to a portion of the remaining kidney was followed by an increased systolic and diastolic blood pressure.

The treatment of infarction of the kidney should be conservative. Surgery will not be indicated except in the unusual case where hypertension develops.

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DIFFERENTIAL DIAGNOSIS OF SOLITARY CYSTIC AREAS IN BONE

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In occasional patients with symptoms of skeletal disease x-ray examination discloses a solitary cyst-like area of rarefaction in bone, unaccompanied by any other perceptible abnormality in physical status, blood cytology, or blood chemistry. Such cases are difficult problems in diagnosis and in therapy. Too often in our experience aspiration biopsy fails to determine the histology of the lesion, so that more and more attention is paid to the clinical history and especially to the details of structure seen on x-ray films. By such means one may limit the probabilities to a surprisingly small number and arrive at a "working diagnosis" before operation.

For purposes of therapy these lesions must be classified into a few major groups, each with its own plan of action, so that unnecessary risk or unnecessary mutilation are avoided as completely as possible. Obviously this is an ideal which cannot invariably be met, but with increasing experience, can be very closely approached. The following Table of Therapeutic Groups is suggested, in each of which examples are given of the more common types of solitary cyst-like lesion.

Group I. Obviously malignant neoplasms.

1. Osteolytic osteogenic sarcoma.
2. Metastatic osteolytic carcinoma, metastatic hypernephroma.
3. Chondromyxosarcoma (or its derivatives).

Group II. Neoplasms of potential malignancy.

1. Chondromyxoma (or its derivatives).
2. Neurofibroma of bone.
3. Fibroblastic tumors of bone.

Group III. Benign neoplasms.

1. Chondroma.
2. Myxoma.
3. Giant cell tumor.
4. Osteoid osteoma.

Group IV. Cystic degeneration (with or without metabolic deposits).

1. Fibrocystic disease (including its several variants of unknown or questionable etiology, e.g., solitary bone cyst, polyostotic fibrous dysplasia).
2. Xanthoma (including localized xanthoma of bone, and diseases of lipid metabolism).
3. Gout.
4. Osteoarthritis (which may show cystic areas especially in the femoral head before joint deformity is apparent).

Group V. Infections.

1. Chronic bone abscess (Brodie).
2. Osteoperiostitis aluminosa.
3. Echinococcus cyst.

4. Staphylococcal osteomyelitis.
5. Tuberculosis (caries sicca).
6. Syphilis (gumma).

It should be noted that among the lesions listed are some which are part of a generalized disease which may, at some stage in its development, present an apparent solitary focus in bone.

The most important qualitative determination required in this type of lesion is evidence concerning malignancy. Two characteristics of malignancy are usually demonstrable on the x-ray film. The first is evidence of rapid development or rapid spread, such as mottling and partial destruction of tissue. The second is evidence that the cortex of the bone has been broken through. Either of these suggests malignancy, but may also occur in rapidly spreading acute infections. The clinical history will usually differentiate the two conditions. Conversely, a clear area, well demarcated, indicates an old, quiescent or slowly developing process. When this is confirmed by an unbroken cortex one is reasonably certain of a benign process.

A clear, well defined, and evenly demarcated cystic area may present a completely vacant appearance (almost glistening in a good plate) or it may show a distinct coarse latticework within it. In the former instance, there is apt to be a sharp border to the cavity; in the latter, the margin is not quite so sharp. In the case of a clear space, bone has been entirely replaced by another tissue, usually cartilage or chondromyxomatous tissue; when trabeculae can be seen, as in the second case, replacement has taken place slowly and consists usually of fibrous, or fibrocartilaginous or fibroxanthomatous tissue. Other lipid or metabolic deposits may present the same appearance.

During the development of these processes, long bones may or may not be found to have expanded in circumference. An expansile lesion does not necessarily indicate malignancy. Polyostotic fibrous dysplasia, for example, causes considerable expansion in bone. Expansion is in many cases a protective reaction in the nature of an osteogenetic attempt to confine a growing lesion. In other cases the expanding osteogenesis may be actually part of a tumor formation. In any event, however, it marks progressive, though not rapid, growth of the pathologic tissue.

Another feature recognizable on the x-ray film is the density of the bone area surrounding the lesion. If it is increased, it signifies protective sclerosis, and one may anticipate a low grade inflammatory lesion, or a slowly growing neoplasm. It may be unchanged in comparison with the rest of the bone, signifying a benign, innocuous lesion. On the other hand, it may be atrophic or porotic from contiguous hyperemia, indicating an active infection. In the writer's experience, the appearance of the periosteum at the level of the lesion is not so instructive as is the texture of the bone itself, and in the case of cyst-like lesions is seldom helpful.

The following outline may serve to systematize the above steps in x-ray interpretation of solitary osteolytic lesions:

1. Rapidity of spread.
 - a. Mottling or moth-eaten appearance of bone surrounding a cystic lesion is indicative of a rapidly spreading process.
 - b. Clear, well demarcated areas indicates slow spread or quiescence.
2. Cortex of the bone.
 - a. When broken or pierced indicates neoplasm infiltrating surrounding soft tissue.
 - b. When unbroken suggests, in the absence of clinical evidence of infection, a benign process.
3. Nature of the cavity.
 - a. Crystal clear appearance suggests a chondroid or myxomatous lesion.
 - b. Clear, but not glistening appearance suggests a simple cystic cavity, probably partly occupied with granulation tissue or old blood.
 - c. Coarse latticework of trabeculae suggests a deposition or substitution lesion (fibrous, xanthomatous, etc).
4. Margin of the cavity.
 - a. Sharp margins indicate a well localized, more or less static process.
 - b. Irregular margins suggest a slowly developing lesion.
 - c. Absence of a definable marginal line usually coincides with the mottling of an infiltrative, and therefore rapidly progressive process.
5. Expansile lesions are slowly progressive: non-expansibility is, in itself, not significant.
6. Reaction of bone in areas contiguous to the cavity.
 - a. Decreased density suggests the presence of active hyperemia.
 - b. Increased density suggests a sluggish process stimulating a protective reaction. This corresponds to a fibrous "walling-off" of similar reactions in soft-tissues.
 - c. Density unchanged from the general texture of the whole bone indicates a static or very slowly progressive, non-productive lesion.
 - d. Mottled areas surrounding the lesion (see Sec. 1).

Note: a and b, or b and d, or a, b and d may be present together, and indicate a lesion producing these respective reactions simultaneously.

When these steps in interpreting the x-ray appearance are added to clinical observations, such as the presence or absence of fever, of loss of weight, of local pain, of history of injury, etc., diagnosis may be greatly simplified. Bone reacts in a fashion comparable to that of soft tissues to some extent. One can infer from x-ray films the "angry" reaction surrounding acute infectious processes, the "protective" reaction around slow growing neoplasms or low grade infections, the "melting away" produced by a highly destructive neoplasm, and the complete "apathy" of surrounding bone in the presence of a benign neoplasm or quiescent abscess.

Three unusual cases treated by the Orthopedic Service within the past year will serve as examples. The first case was that of a woman, 48 years of age, who was admitted with a history of generalized rheumatic pains for fifteen years and recurrent sharp pains in the lower half of the left forearm of four years' duration. The admission diagnosis was rheumatoid

arthritis, but because of the severity of pain in the forearm, an x-ray examination of this area was ordered (fig. 1). This disclosed a subcortical, solitary, cystic lesion of the ulna about one inch above the styloid process. Upon analysis, it was found to fit into the following pattern: 1) Texture crystal clear, well demarcated; 2) cortex unbroken; 3) margins rather sharply drawn; 4) growth not expansile; 5) surrounding bone without reaction. These findings indicated a static or very slowly progressive lesion. The moderate local tenderness, the absence of local heat, or systemic fever, and the sharpness of the margins presumptively excluded an



FIG. 1. X-ray examination revealed a subcortical, solitary, cystic lesion of the ulna about one inch above the styloid process.

infectious process. The crystal clear appearance of the lesion in the x-ray film indicated a chondroid or myxomatous lesion. In spite of the rarity of chondroma or myxoma in this part of the skeleton, a working diagnosis of benign chondroid or myxomatous tumor was made and operation advised. The location of the lesion at the lower end of the ulna made resection feasible without significant deformity or dysfunction. Because of the fear that surgical trauma to a benign chondroma or myxoma may provoke malignant metaplasia or at least recurrence, the lesion was removed intact by resection of the ulnar styloid and lower shaft was

performed. Subsequent pathological examination confirmed the diagnosis. In this case, the lesion was so clearly placed in a "therapeutic" category, that no alternative procedures had been planned.

The second case, a girl of 12, was admitted to the Orthopedic Service with a painful mass over the sterno-clavicular joint of one year's duration. A recent injury had caused exacerbation of the pain and swelling. X-ray examination (fig. 2) disclosed a large cystic area involving the sternal end of the left clavicle. A coarse trabecular latticework extended through the entire area. The cortex was broken in a manner indicating fracture rather than extrusion of growing tissue. There was no significant sclerosis of the



FIG. 2. X-ray examination disclosed a large cystic area involving the sternal end of the left clavicle.

surrounding bone, but an ill-defined margin could be distinguished. In view of the location of the epiphyseal area of the bone and the age of the patient these x-ray characteristics suggested a giant-cell tumor, but because of the pathological fracture one could not eliminate the possibility of a more malignant lesion. Moreover, giant-cell tumors are extremely rare at this site.

This case was placed into group III, with the possibility of group II in mind. In either instance, surgery was indicated. Frozen section studies were arranged for at the time of operation, not so much for accurate histologic diagnosis, but to determine the possible presence of malignancy.

The pathologist diagnosed the frozen section tissue as belonging unequivocally to the giant-cell tumor group, and therefore the lesion was thoroughly curetted, but no resection was made. Further pathologic study confirmed the diagnosis.

The third case is an example of another application of the advantages of therapeutic grouping. In this case, the actual diagnosis proved to be wrong, but because a proper grouping had been arrived at, the treatment was correct. A boy, age 7, was admitted to the Orthopedic Service because of a solitary cystic lesion discovered in his right calcaneus. There was a history of recent injury and some local tenderness. The x-ray film (fig. 3) showed an obviously benign lesion, with little or no surrounding bone reaction, a clear matrix and questionable trabecular lattice-work. Because of the local tenderness, a working diagnosis of quiescent abscess activated by recent injury was made. This placed the lesion in group V. Its central



FIG. 3. X-ray examination disclosed an obviously benign lesion, with little or no surrounding bone reaction, a clear matrix and questionable trabecular lattice-work.

location and clear margins, the absence of surrounding tissue involvement, and the negative Wassermann reaction eliminated other considerations within the group. However, certain members of group III or IV could not be altogether eliminated. In either case the therapeutic indication was for exploration, curettement, and, because of the large size, the use of bone chips from the tibia. No alternative procedures were entertained because none were indicated by the grouping. Pathological study of the tissue showed a distinct myxomatous structure. Hence the diagnosis was myxoma of bone. This lesion is most unusual, and, in the calcaneus, extremely rare.

CONCLUSIONS

Three rare lesions producing solitary cystic areas in bone were recently admitted to the Orthopedic Service. The diagnosis of such lesions presents

a complicated and frequently insoluble problem. Too often aspiration biopsy is inefficient and diagnosis must rest upon clinical and x-ray studies. These lesions are shown to fall into a relatively simple series of groups when considered from the therapeutic viewpoint, even though their histology may differ greatly. When so considered, the surgeon is usually enabled to plan his operative approach intelligently. Secondary operations can thereby often be avoided, and conversely unnecessarily mutilating operations can be forestalled. Frozen section studies at the operating table are indispensable when one evaluates their purpose properly. They cannot be depended upon to certify a histologic diagnosis or grade of malignancy; they may be depended upon to specify the presence of active malignancy or the absolute or relative benignancy of a given lesion.

INCIDENCE OF HYPERTENSION IN PEOPLE OF FORTY YEARS OF AGE AND OLDER

ARTHUR M. MASTER, M.D., AND SIMON DACK, M.D.

[From the Cardiographic Laboratory and the Services of The Mount Sinai Hospital]

It has been our impression during the last few years that the incidence of hypertension in the general population over the age of 40 is considerably higher than has been suspected. We pointed this out recently (1) when, in an attempt to evaluate the importance of hypertension in the etiology of coronary artery occlusion, it was necessary to compare the prevalence of hypertension in the middle aged and older persons in the general population with that of patients with coronary occlusion. From the data of several published reports we calculated that the incidence of hypertension in 42,000 persons was approximately 26 per cent at the age of 55 and 45 per cent above the age of 65.

The problem now assumes even greater importance since the population is aging rapidly. According to a recent New York Department of Health Bulletin (2) the following is a picture of the New York City population from the years 1900 to 1940 by ten year periods:

PERIOD	45-64 YEARS	65 AND OVER
1900	13.1%	2.8%
1910	13.7	2.8
1920	16.0	3.1
1930	17.3	3.8
1940	21.8	5.5

Actually, in 1940 more than a fourth of the population was over 45 years of age and of course the number beyond 40 would be larger still.

The present report is based on an analysis of the blood pressure of 5,686 consecutive patients admitted to The Mount Sinai Hospital between 1938 and 1941. Our procedure was to copy the blood pressure on the charts of patients in a consecutive order, male and female, over 40 years of age, including those on medical, surgical or specialty wards. If more than one reading was recorded we took the average and if only one observation was recorded we accepted it as it appeared. The auscultatory method was used in the hospital, the diastolic pressure being usually the first disappearance of sounds although undoubtedly many took the fifth phase, i.e., the complete disappearance of sound. A systolic level of 150 mm. Hg. or more and a diastolic level of 90 mm. Hg. or more was classed as hypertension.

Results. The 5,686 patients studied were about equally divided between the sexes (Table I). In the years 40 to 49 the incidence of hypertension,

i.e., a blood pressure of 150 systolic and 90 diastolic or more, was about 32 per cent; in the decade 50 to 59, 42 per cent for men and 51 per cent for women; and for 60 to 69 years, 47 per cent for men and 63 per cent for women. As is well known there is thus a higher incidence of hypertension

TABLE I

Incidence of hypertension in males and females forty years of age and over

AGE GROUP	SEX	NUMBER	HYPERTENSION
40-49	M	832	32%
	F	1291	33%
50-59	M	965	42%
	F	911	51%
60-69	M	672	47%
	F	490	63%
70-89	M	329	52%
	F	196	62%
Total	M	2798	42%
	F	2888	48%
		5686	

TABLE II

Percentage of patients admitted for hypertension and its complications

(Based on analysis of 300 hypertensive males and females in each decade)

AGE GROUP	SEX	ADMITTED FOR HYPERTENSION
40-49	M	2.0%
	F	3.5%
50-59	M	5.2%
	F	7.7%
60-69	M	3.2%
	F	5.3%
70-79	M	4.8%
	F	8.5%

in women; over 50 years more than half have hypertension. These figures are distinctly higher than those obtained from the few available published reports.

Comment. It might be thought that hospital patients have an inordinately high prevalence of hypertension and in order to gauge the impor-

tance of this we sampled 300 male and female patient cards of the hypertensive group in each decade (Table II). It may be seen that of all the patients who had hypertension only a very small percentage was admitted for this or for an illness referable to the hypertension. We included the complications of high blood pressure such as cerebral hemorrhage, heart failure in a hypertensive patient, etc. It might be considered unjustifiable to accept a single blood pressure reading of 150 systolic and 90 diastolic or even 160 systolic and 100 diastolic as evidence of hypertension. However, we accepted readings as low as 80 systolic and 60 diastolic in patients in shock or post-hemorrhage. In other words, single low readings balanced the high. Nor is the atmosphere of a hospital with its seriously sick patients and the presence of doctors and nurses to be given too much consideration. Patients at The Mount Sinai Hospital practically always receive some medication to allay unrest and to assuage pain, i.e., sedatives and opiates. Moreover, the large majority of our patients had many readings taken over a period of days and weeks. To further evaluate the accuracy of single readings like 150 systolic and 90 diastolic we have had many patients return for a follow-up examination. In at least three-quarters of the cases the blood pressure was still high and usually greater than the original figure. This will be described in more detail in a later publication.

As a check on the validity of our results we have determined the incidence of hypertension in persons employed in industry and those residing in homes for the aged. The former group presented a slightly lower incidence of hypertension than we have cited but it is probably a selected group. In the homes for the aged there is decidedly a higher incidence than in our hospital group. These results are probably too high to be applied to the general population but nevertheless these two groups give us added assurances that the hospital blood pressure readings we have obtained are applicable to the general population as a whole.

It now appears that the adage of twenty years ago that the systolic blood pressure should be 100 plus the patient's age is not entirely wrong. It would be correct perhaps if modified to say that a systolic blood pressure equal to 100 plus the patient's age may not be abnormal for him.

The demonstration of the increasing incidence of hypertension with age does not necessarily indicate that the increased blood pressure is normal (i.e., not pathological). It merely means that such abnormalities as hypertension are common in the aged, and may in fact be part of the aging process. The relationship of such hypertension to mortality rate cannot be determined from these studies.

SUMMARY

Hypertension, i.e., a systolic blood pressure of 150 mm. Hg or more or a diastolic blood pressure of 90 mm. Hg or more, is very common in patients forty years of age or older admitted to The Mount Sinai Hospital.

In the fifth decade hypertension is present in 32 to 33 per cent, in the sixth decade in 42 to 51 per cent, in the seventh decade 47 to 63 per cent, the first number applying to men, the second to women.

Reasons are given to show that our findings hold for the general population in the country. The incidence of abnormally high blood pressure increases progressively with age in people over 40 and may be part of the aging process.

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CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D., *presiding*

Monday, February 10, 1941

Case 4. Multiple Brain Abscesses*

[From the Surgical Service of Dr. H. Neuhoof]

History (Adm. 448799; P.M. 11359). A nurse, aged 29 years, attempted suicide by hypodermic injection of morphine and one hour and a half later was brought to another hospital in coma. She was given artificial respiration, inhalations of carbon dioxide and stimulants. While being treated, she coughed up large amounts of blood-tinged frothy sputum. She regained consciousness about sixteen hours later. During that period her temperature rose to 102°F. and numerous râles were heard over the right upper chest. She improved gradually and left the hospital four days later, still coughing and, at times, bringing up blood-streaked sputum. One month after the suicidal attempt her sputum became profusely bloody and foul smelling. Her temperature became elevated and she had dyspnea. She returned to the hospital and remained there for almost one month, during which time her temperature remained elevated, reaching as high as 105°F. She expectorated large amounts of foul sputum, at times as much as ten ounces in one day. A culture of the sputum revealed anaerobic streptococci. The white blood count was increased. She was treated with sulfapyridine and given several blood transfusions without appreciable change in her condition, and she was brought to this hospital on November 16, 1939, two months after her suicidal attempt.

Examination. She appeared to be acutely ill, somewhat emaciated and dyspneic. Her temperature was 100.4°F. and her pulse rate was 90 per minute. There was some clubbing of the fingers. Dullness was noted on percussion over the right upper chest, shoulder and back. Numerous râles were heard anteriorly and high in the right axilla.

Laboratory Data. Blood: Hemoglobin, 69 per cent; white cell count 20,000 with 81 per cent polymorphonuclear leucocytes. An x-ray examination of the chest showed infiltration of the right upper lobe with large cavities in the apex and in the paravertebral segment of the right upper lobe. There was also an infiltration of the left upper lobe.

Course. A thoracotomy was performed on the day of admission. A large trilobular putrid abscess was found in the lung after excision of the fourth rib posteriorly on the right side. A large bronchial fistula was established and the loculations were packed in the usual manner. On the fifth postoperative day her temperature rose to 104.2°F.; her pulse rate became rapid, and her sputum was bloody. The hemoptysis was so copious that it was found necessary to revise the wound in the operating room.

* The first three cases were reported in previous issues of the Journal (Vol. VIII, Nos. 3, 4).

Active bleeding was found in the region of a large bronchial fistula. Her hemoglobin dropped to 43 per cent and a transfusion was given. Her condition remained fairly satisfactory for four days although moderate fever persisted. On the fifth day after the second operation her temperature rose to 106°F. Signs of pneumonia were detected in the left lower lobe. Sulfapyridine was administered for two days and a blood transfusion given. Her general condition improved and she was allowed out of bed in a few days. Eighteen days after the pneumonotomy her temperature rose to 103°F. and a large tender swelling was noted in the left posterior axillary region. This was incised and drained. Twenty days later, a large abscess containing foul, thick pus was found under the musculature of the chest wall and incised. On culture, the pus yielded *streptococcus hemolyticus*, *streptococcus viridans*, aerobic diphther-

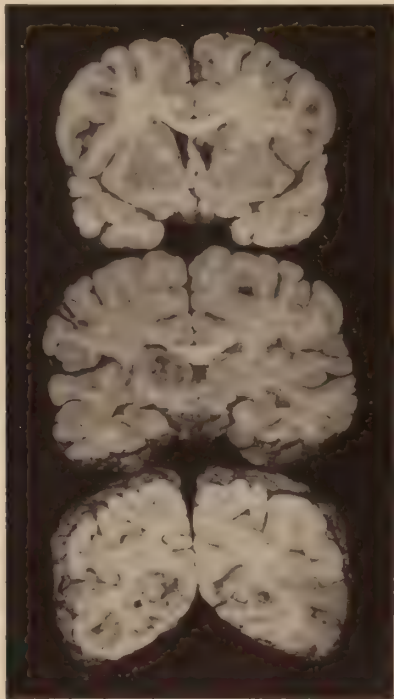


FIG. 14. Gross appearance of coronal sections of the brain in case 4 showing multiple brain abscesses with the largest one displaying a well formed capsule.

roids and anerobic gram negative bacilli. Five days after the drainage of this abscess, the patient complained of severe headache. Convulsive seizures and distinct meningeal signs developed quickly. Stiffness of the neck, hyperactive deep reflexes, a suggestion of bilateral patellar clonus, bilateral Hoffman and Kernig signs were recorded. A lumbar puncture yielded turbid cerebrospinal fluid under increased pressure, containing 20,000 white blood cells per cubic millimeter. On smear, the cerebrospinal fluid showed gram positive cocci, and on culture hemolytic streptococci were found. A blood culture was sterile. The patient died several hours after the onset of meningitis.

Necropsy Findings. General. Gross. Subacute abscess of the left chest wall; subacute lung abscess, right upper lobe; acute hematogenous osteomyelitis of the right femur; pulmonary edema and congestion of the right lower lobe and left lung.

bronchopneumonia, left lower lobe; ascites and bilateral hydrothorax; fatty and parenchymatous degeneration of the liver.

Brain. Gross. The dura stripped easily. There was a moderate increase in the amount of cerebrospinal fluid. In the cisterna magna and inter-peduncularis there was greenish-yellow purulent fluid. The brain was somewhat softer than normal. The superficial veins of the dura of the spinal cord were dilated and tortuous. This was most marked in the cervical and lumbar regions. There was a large amount of cloudy subarachnoid fluid. The pituitary gland was normal.

On section of the brain the following was noted: 1) Several abscesses varying in size from 0.5 to 1.0 cm. in diameter. They were distributed chiefly in the subcortex of both hemispheres. The left pulvinar was almost entirely replaced by a large abscess (fig. 14). The abscesses were well demarcated and encapsulated, suggesting their existence for some time. 2) There was a widespread ependymitis, more marked in the posterior horn of the right lateral ventricle. The choroid plexus of the right lateral ventricle was swollen and covered with exudate.

Gross Diagnosis. Multiple, metastatic brain abscesses, ependymitis and diffuse purulent meningitis.

Microscopic. Sections of the cortex and of two of the abscesses were stained with hematoxylin and eosin. One of the abscesses was round, about 7 mm. in diameter, and lay about 1 cm. below the surface of the cortex. This abscess contained necrotic debris in its wall and was surrounded by a thick capsule consisting of fibrous tissue and elongated cells. Surrounding the capsule was a zone of increased vascularity. The cortex adjacent to this abscess was extensively infiltrated with glial elements and the neurones in the cortical layer showed a variety of degenerative changes. The vessels in the entire section were surrounded by accumulations of glia cells. The meninges were normal. The other abscess was serpiginous in shape, was about 2 cm. in length, and had a very thin wall. The accumulation of glia was more extensive and extended widely into the surrounding brain tissue. The vessels were engorged in the nearby brain tissue and surrounded by a large accumulation of glial elements.

Diagnosis. Multiple brain abscesses.

Comment. Dr. Globus: In this case little need be said except that here, as in other instances, multiplicity of abscesses point to their metastatic character. What particularly merits comment is the probability that the brain abscesses were most likely formed here by reason of the introduction of highly infective material into a branch of a pulmonary vein during the attempt of the surgeon to check the bleeding from the bronchial fistula.

Reported by A. Zitani, M.D.

THE STORY OF THE MOUNT SINAI HOSPITAL

*Beginning with this issue, the Journal will carry in a series of installments the story of The Mount Sinai Hospital during the ninety years since it was founded. Offered in celebration of the Hospital's ninetieth anniversary, these historical notations will in a way reflect the course of medicine in New York and elsewhere since 1852, and the changing background of its development. The narrative has been compiled by Miss Jane Benedict from hospital archives, personal and professional correspondence, medical and historical literature, and extensive interviews with those who have been both eye-witnesses and agents of its progress. It is offered, not as a definitive history of the Hospital, but rather as source material from which a history will later be written. Corrections will be welcomed if errors of fact or interpretation are discovered. Additional information which may help to make the picture more complete will be appreciated.**

In this installment the founding of the Hospital is described and its founders are depicted. The social factors which made such an organization a needed and welcome addition to old New York are sketched.

THE FORMATIVE YEARS. 1852-1872

I

When Sampson Simson and his eight associates founded the Jews' Hospital in New York, parent of the modern Mount Sinai, they were giving form and substance to what had long been a hope of the Jewish community. The Jews of New York were active citizens in a city which was experiencing the growing pains of the Industrial Revolution. Only the year before the founding of the Hospital a railroad line had been completed between New York and Dunkirk on Lake Erie. An already industrial population was being daily increased by the hordes of immigrants who poured in from Europe. The census of 1850 revealed that of 515,547 men and women in New York, 83,620 were employed in 3,387 factories.¹ In the efforts to cope with problems arising from New York's development as a trade center, the Jews played an energetic part.

Their communal rôle dated from 1654, when a group of Jews had emigrated to New Amsterdam from Brazil, in order to escape the persecution of Brazil's Portuguese conquerors. Upon their arrival in the American colony, the home government of Holland passed the Act of Toleration stating that the Jews might remain provided they cared for their own poor. From that time on, the Jews of New York effectively organized charitable work among their people. At first directly through the synagogues, and later through independent organizations cooperating with the synagogues, Jewish charity cared for the aged, the orphaned, and the destitute. It provided free education and taught the needy a trade with which to help themselves. It formed societies to attend the sick and dying, and to visit poor homes invaded by disease.

These worthy efforts were made against overwhelming odds. With the

* Corrections or additions may be addressed to the *Historian of the Hospital*.

¹ WILSON, JAMES GRANT: *Memorial History of the City of New York*, New York Historical Company, 1893, Vol. 4.

swiftly increasing influx of immigrants, many of whom were forced by circumstance to live in the frightful slums of that period, to give adequate care to the ill in the midst of destitution proved almost impossible. Many Jews were thus in urgent need of hospitalization. There were, of course, city hospitals—like Bellevue—in which such patients were welcome; but there was no institution sponsored and supported by the Jewish community itself. This lack was felt ever more keenly by the Jewish population as time went on.

A determination to meet this need was announced in 1850 by the Hebrew Benevolent Society, on the occasion of its twenty-ninth anniversary, when the



SAMPSON SIMSON

President of the Jews' Hospital in New York, 1852-55

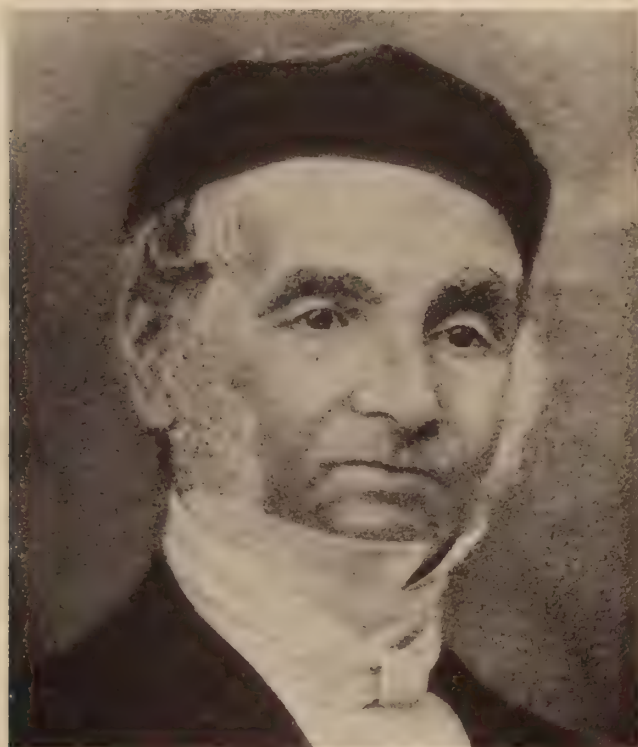
Directors of that Society declared that "... the surplus funds safely invested will shortly enable us to adopt preliminary measures for the establishment of a Jewish Hospital, the great and final object of our institution."² In the course of the following year, 1851, the same organization called a conference of charitable societies, and definite plans were formulated for the founding of a hospital as soon as there were sufficient funds.³

² Invitation to Twenty-ninth Anniversary Celebration, Hebrew Benevolent Society, 1850. (In possession of the American Jewish Historical Society.)

³ A Plan for the Institution of a Hospital for the Sick and Aged, 1851. (In possession of the American Jewish Historical Society).

While their plans did not go into effect, they nevertheless served to prepare the ground for future action. Accordingly, when Sampson Simson and his eight associates incorporated the Jews' Hospital in New York on January 15, 1852, they found the Jewish community ready to extend full cooperation.

The group that Sampson Simson had gathered about him were old friends. They knew each other well and had worked together in previous charitable undertakings. This group included, in addition to the venerable Simson, the Rev. Samuel M. Isaacs, John I. Hart, Benjamin Nathan, John M. Davies, Henry



REV. SAMUEL M. ISAACS

Director of the Jews' Hospital in New York, 1852-56; Vice-President, 1856-57

Hendricks, Theodore J. Seixas, Isaac Phillips, and John D. Phillips. These nine men signed the incorporation papers and were the first Directors of the Hospital. They held their first meeting in the Trustees' Room of the "Synagogue in Crosby Street," home of Shearith Israel, the oldest Jewish congregation in America.

Sampson Simson, then seventy-two years old, was elected their President. Graduated from Columbia College in 1800, he later studied law under Aaron Burr, and was probably the first Jew admitted to the New York Bar.¹ Unmar-

¹ ISAACS, MYER S.: Sampson Simson. Publications of the American Jewish Historical Society, No. 10, 1902.

ried, reserved, preferring country life on his Yonkers estate to the growing bustle of New York, he was the patriarchal figure of his sister's family. He wore the picturesque costume of an earlier day—even to knee breeches and buckles—had long white hair, old-fashioned, over-sized spectacles, and carried a silver-headed cane upon which he was in the habit of leaning when seated.

One can well imagine the gravity with which these deeply religious and public-spirited men heard their President call the meeting to order and read the articles of incorporation which stated, "... we have associated and hereby do associate ourselves into a benevolent, charitable and scientific Society . . . to be known as 'The Jews' Hospital in New York'." The minutes of that meeting record that having read the articles of incorporation, "The President . . . declared the Society organized for the purposes therein stated" which were "... medical and surgical aid to persons of Jewish persuasion and for all other purposes appertaining to Hospitals and Dispensaries . . ."

The articles of incorporation read in part as follows:

"We Sampson Simson, Samuel M. Isaacs, John I. Hart, Benjamin Nathan, John M. Davies, Henry Hendricks, Theodore I. Seixas, Isaac Phillips, and John D. Phillips, Citizens of the United States of America and the State of New York and Residents of the City of New York, County of New York and State aforesaid, being each over Twenty-one years of age and desirous of associating ourselves (with such persons as may hereafter be admitted as members for benevolent, charitable and scientific purposes in conformity with and under the provisions of an act of the State of New York entitled "An Act for the incorporation of benevolent, charitable, scientific, and missionary Societies," passed April 12, 1848 Certify that We have associated and hereby do associate ourselves into a benevolent, charitable and scientific Society to be known and distinguished in law, or otherwise by the name of "The Jews' Hospital in New York," that the particular business purpose and object of such association and Society will be medical and surgical aid to persons of the Jewish persuasion; and for all other purposes appertaining to Hospitals and Dispensaries; that the said Society will be under the management and control of Nine Directors: that Sampson Simson, John I. Hart, Benjamin Nathan, Henry Hendricks, Samuel M. Isaacs, John M. Davies, Theodore I. Seixas, Isaac Phillips and John D. Phillips shall be the Directors of such Society for the first year of its existence; and that the said Sampson Simson shall be the President; the said John I. Hart, Vice President; the said Benjamin Nathan, Secretary; and the said Henry Hendricks, Treasurer of the said Society for the first year. And that the place of business of the said Society will be in the city, County, and State of New York."

It was with a profound sense of responsibility that these men established the first Jewish Hospital in the United States. The enterprise was consistent with their own records as energetic citizens in a rapidly growing city, and with a long tradition of active participation in the life of the community. One of their number was a descendant of the Rev. Gershom Mendez Seixas who during the Revolution had persuaded the very congregation in whose building this group was meeting, and of which some were members, to close the doors of their synagogue rather than remain in New York after it had fallen into the hands of the British.⁵ He himself went to Philadelphia and took up religious duties, while other members of the Portuguese Congregation scattered to various sections of the country.

⁵ PHILLIPS, CAPTAIN N. TAYLOR: *The Congregation Shearith Israel*, Publications of the American Jewish Historical Society, No. 6, 1898.

We Sampson Jones Samuel W. Jones John
 West Benjamin Nathan John M. Davis Henry
 Windrock Theodore I Lewis Isaac & Phillips and
 John D. Phillips Citizens of the United States of Amer-
 ica and of the State of New York and Residents of the City
 of New York Legals of New York and State aforesaid being
 each one Twenty one years of age and desirous to incor-
 porate (incorporated) with such persons as may hereafter be ad-
 mitted as members for benevolent charitable and scientific
 purposes in conformity with and under the provisions of
 an act of the State of New York entitled "An Act for the
 incorporation of benevolent charitable scientific and mag-
 istrate societies" passed April 12 1855 Certify that We
 have and hereby do separate ourselves into a benevolent char-
 itable and scientific Society to be known and distinguished
 here as otherwise by the name of "The Jews' Hospital"
 in New York that the particular business purpose and
 object of such association and Society will be medical and
 surgical aid to persons of the Jewish persuasion and for
 all other purposes appertaining to Hospitals and Charities
 and that the said Society will be under the management
 and control of Nine Directors that Sampson Jones
 John West Benjamin Nathan Henry Windrock
 Samuel W. Jones John M. Davis Theodore I
 Lewis Isaac & Phillips and John D. Phillips shall
 be the Directors of such Society for the first year of its
 existence and that the said Sampson Jones shall be
 the President the said John West Vice President
 the said Benjamin Nathan Secretary and the said Henry
 Windrock Treasurer of the said Society for the first Year
 And that the place of business of the said Society will be in
 the City County and State of New York

In Witness whereof We have hereunto set
 2-1

The Simson family went to Danbury, Connecticut, and it was there that Sampson Simson was born in 1780.⁶ The greater part of his life Sampson Simson was active in philanthropic work, giving generously and judiciously of his very considerable wealth. In choosing the objects of his philanthropy, he depended greatly upon the advice of the Rev. S. M. Isaacs. The latter, the rabbi of the Congregation Shaaray Tefila, was born in Holland in 1804, but grew up in England. In 1839 he was called to the United States as rabbi of the Congregation B'nai Jeshurun. Somewhat later he became the leader of Shaaray Tefila when that group, in 1845, split off from the older congregation.⁷ From the time he arrived in this country, he was the guiding spirit of New York philanthropy among the Jews. A ruddy-faced, pleasant man, he knew and liked many people in various walks of life. He was popular and always in great demand, especially with young folk. But above all he was fond of his immediate family circle, often singing old English folksongs with his children.⁸ A defender of the older and stricter forms of his religion, he was nevertheless tolerant of other views. He was a sincere and honest minister, always ready to help others, to take part in organizing a new charity, and to speed in the middle of the night on a visit to the distressed or the dying.

Associated with Rev. Isaacs in the Congregations B'nai Jeshurun and Shaaray Tefila were John M. Davies, John D. Phillips, and John I. Hart, who was elected Vice-President of the new Hospital. Hart had been one of the committee which, in 1825, requested and received aid from the Portuguese Congregation in founding B'nai Jeshurun.⁹ John D. Phillips was active in the fur business and also dealt extensively in real estate.¹⁰ He was one of those who had sufficient foresight to visualize a New York which might extend beyond its then northern limit of Thirty-fourth Street, and include the rural villages of Bloomingdale, Yorkville, and Manhattanville. These sections, in 1852, could be reached only by horse and carriage over rutted country roads. But John D. Phillips bought large holdings in the neighborhood that is now Fifty-seventh Street, and became one of the early and enthusiastic promoters of uptown New York.

Benjamin Nathan, first Secretary to the Hospital; Henry Hendricks, its first Treasurer; Theodore J. Seixas and Isaac Phillips, were all members of the historic Portuguese Congregation, Shearith Israel, founded in 1655.¹¹ Benjamin Nathan was a member of the New York Stock Exchange; Henry Hendricks was an owner of Hendricks Brothers Copper Rolling Mill, one of the oldest firms¹² in the United States; Isaac Phillips was Appraiser of the Port of New York, City Commissioner of Education, and a President of the Portuguese Congregation.¹³ Theodore J.

⁶ ISAACS, MYER: Sampson Simson, Publications of the American Jewish Historical Society, No. 10, 1902.

⁷ The Jewish Messenger, January 6, 1882.

⁸ Interview with Miss Miriam Isaacs, daughter of Rev. S. M. Isaacs, June 7, 1938.

⁹ PHILLIPS, CAPTAIN N. TAYLOR: The Congregation Shearith Israel, Publications of the American Jewish Historical Society, No. 6, 1898.

¹⁰ Interview with Mr. Lewis Phillips, grandson of John D. Phillips, June 16, 1938.

¹¹ Interview with Captain N. Taylor Phillips, son of Isaac Phillips, June 15, 1938.

¹² Interview with Mr. Henry Hendricks, great-grandson of Henry Hendricks, June 24, 1938.

¹³ See footnote 11.

Seixas and Henry Hendricks had worked together the previous year at the conference called by the Hebrew Benevolent Society to plan the founding of a Hospital.¹⁴

The crowded conditions in the slums, accompanied by destitution and crime which paralleled the rapid industrial growth of the city during the period between the 1840's and 1870's led to the founding of many charitable institutions. Churches and Sunday Schools turned their attention to social work, aiming at the rehabilitation of those whom life in the slums had warped. With the increasing spread of disease, due to unhygienic conditions in the overcrowded tenements, the need for more hospitals became imperative. It was during this period that the Association for the Improvement of the Condition of the Poor came into existence; that the Young Men's Christian Association, the Children's Aid Society, the Society for the Prevention of Cruelty to Children, were organized; and that St. Luke's Hospital, the Hospital for the Ruptured and Crippled, and the Roosevelt Hospital were established. The Jews' Hospital was a part of this trend to improve the lives of the unfortunates forced to live in the slums.

The step was a courageous one as can be sensed from a statement by the Hospital Board published some years later, which in retrospect described the financial condition of the Jews' Hospital Society when it was first formed:

"The history of the Hospital is the history of most of our benevolent institutions. With no other endowments than the impulsive and limited donations of their charitable and religious originators—with no other revenues than that hoped for from the free-will offerings of their friends and associates—they are organized, established and set in operation, wherever and as often as their usefulness is suggested, or their necessity felt."¹⁵

It was thus with no assurance of what money might be forthcoming that the Jews' Hospital in New York came into being. So urgent was the need for such an institution that the founders felt the effort must be made.

It was particularly encouraging, therefore, that at the first meeting of the Board, the second order of business should be a letter announcing a substantial donation. It was signed by Barrow Benrimo, chairman of a group called the Young Men's Committee, which on February 4 of 1852 had given a ball for the benefit of the Jews' Hospital Society. This donation of \$1,034.16 was the initial contribution to the Hospital, the proverbial shoestrapping on which it started. A resolution of thanks for "their laudable and successful efforts in commencing in a liberal degree the establishment of a fund to carry out the objects of this institution" was passed and sent to the members of the Committee, which included Barrow Benrimo, Samuel A. Lewis, L. H. Simpson, George Henriques, Adolphus S. Solomons, Rowland Davies, Max Bachman, George King, L. Bierhoff, Noah Content, Henry Honig. That this group was particularly interested in helping the Hospital is not surprising, since the year before its chairman, Barrow Benrimo, had been a delegate to the conference called by The Hebrew Benevolent Society to discuss the possibility of a Hospital.¹⁶

¹⁴ A Plan for the Institution of a Hospital for the Sick and Aged, 1851. (In possession of the American Jewish Historical Society).

¹⁵ The Occident, Isaac Leeser, editor. Vol. 14, p. 397 (November) 1856.

¹⁶ Plan for the Institution of a Hospital for the Sick and Aged, 1851. (In possession of the American Jewish Historical Society).

Another member of the Committee, Adolphus S. Solomons, in reminiscing some twenty years later, described a visit he had made in 1851 to a Jewish hospital in Frankfort-on-Main. He told of the shame he had felt when he had to admit that there were no such hospitals in the United States, and how he "then and there determined that, God willing, such a reproach upon his native land should not long exist, if he could do aught to prevent it . . ."¹⁷ A year later came the opportunity to do considerably more than "aught". He contributed materially toward the proposed Jews' Hospital, and his support continued after it had become a fact. As an older man and an active citizen of Washington, D. C., he was to show his interest in medical aid, not only by assisting in the organization of the American Red Cross, but also by his part in the development of the Garfield, Columbia, and Providence Hospitals.¹⁸

The first problem facing the young Society was to obtain a place in which their Hospital could be set up. A committee was appointed at the second meeting of the Board to find a building that could be used as temporary quarters. At the third meeting, this group reported that it had found a house which could be rented for nine months for one hundred and twenty-five dollars; it was voted to accept this offer. A month later, however, a special meeting was called to announce that Sampson Simson "had executed a deed to the Jews' Hospital in New York for a lot of land on the south side of Twenty-eighth Street between Seventh and Eighth Avenues, 25 feet front and rear by about 98 feet more or less."¹⁹ The Board immediately set about securing appropriate plans for the erection of a Hospital on this piece of land.

In 1852, Twenty-eighth Street was far beyond the bustle of the city. The surroundings of the site were sufficiently rural to allow the picking of tomatoes, the building of bonfires, and the roasting of potatoes.²⁰ At that time the fashionable sections of the city were Bond Street, Washington Square, and East Broadway, where the red brick homes of wealthy citizens lined the thoroughfares.²¹ Those streets that were not dirt roads were paved with cobblestones.²² Illumination was furnished by gas, which had been introduced into New York only twenty-nine years before the founding of the Hospital.²³ Transportation depended on horses or on one's own two feet. Sampson Simson, living on his estate in Yonkers, must have considered the trip to New York a formidable journey when he set forth in a horse and carriage to jolt his way over the rutted country roads that led to the city.

In the first month of the Society's existence, a constitution was drawn up and sent with a circular to those who might be interested. The circular declared that

¹⁷ SOLOMONS, ADOLPHUS S.: "Some Scraps of History Concerning Mount Sinai Hospital," *Jewish Messenger*, Rev. S. M. Isaacs, Editor, Vol. 3, No. 23, (December 17) 1875.

¹⁸ MARSHALL, LOUIS: Adolphus S. Solomons, *Publications of the American Jewish Historical Society*, No. 20, 1912.

¹⁹ Minutes of Board of Directors' Meeting, Jews' Hospital, October 20, 1852.

²⁰ MEYER, ALFRED: "Recollections of Old Mount Sinai Days," *Journal of The Mount Sinai Hospital*, Vol. 3, No. 6, 1937.

²¹ WILSON, JAMES GRANT: *Memorial History of the City of New York*, New York Historical Company, 1893, Vol. 4.

²², ²³ See footnote 21.

"from the mere dues of members, but an insufficient sum can be obtained; it is therefore incumbent on the Directors at once to call on those who have the ability, to enable them to carry out the objects of the Society." The dues mentioned were five dollars a year and entitled one to a voting membership. The circular expressed also the hope of setting up the temporary Hospital as indicated before, but this intention was soon abandoned; energy and money were concentrated on the erection of the Twenty-eighth Street building.

Donations were not long in coming. In this connection it is interesting to note the intimate character of this group which formed the Hospital's early supporters—the family relationships, the associations with each other and with the charitable and religious work which had led to the Hospital's creation. The minutes of Board meetings for the years 1852 and 1853 indicate that the Directors were prompt contributors. So meticulous are the records of those early days that we are told that Sampson Simson paid a bill of \$61.86 for the Society and allowed it to stand as a donation. Lewis M. Morrison and Joseph Fatman, the one to be elected a Director three years later and the other after five years, both helped to support the young organization. Mrs. Frances Hendricks and Selina Hendricks, the mother and sister of Henry Hendricks, each gave five hundred dollars, with the promise that if five thousand dollars were collected within one year, each would repeat the donation. The name of George Henriques on the list of contributors indicates that members of the Young Men's Committee of some months before maintained their interest in the founding of a Jewish hospital. Rev. J. J. Lyons, rabbi of the Portuguese Congregation, and Rev. Ansel Leo of the B'nai Jeshurun Congregation, who had married Sampson Simson's niece, were included in these records. The familiar family names of Seixas, Hart, Nathan, Henriques, Morrison, and Davies appear frequently, indicating the extent to which entire families were interested. That the community as a whole was also sympathetic with the move is indicated by the donation of two hundred and fifty dollars from "A Priest".

The Board divided into groups to solicit funds from the various congregations. M. Hendricks Levy paid one hundred dollars as a life member of the Society and offered his services in collecting funds on a trip "through several of our states." By April of 1853, the Board decided that when the seven thousand dollar mark was reached, the Building Committee should be authorized to "enter into contracts according to specifications." By October 2 of that year, Mrs. Hendricks and her daughter were notified that five thousand dollars were in the hands of the Treasurer and as the records show, they fulfilled their promise by contributing a second five hundred dollars each.

On October 30, 1853, the Building Committee reported that the mason had started digging and that in ten days he would be prepared for the laying of the cornerstone.

The next installment will begin with the laying of the cornerstone, and will carry the story to the dedication of Mount Sinai's first home.

James Speyer
July 22, 1861—October 31, 1941

The members of the Hospital Staff have learned with deep sorrow of the death of James Speyer, who has been a member of the Board of Trustees since 1902. Mr. Speyer was a loyal friend of the institution throughout this entire time and much of the progress of the Hospital was made possible through his generosity. He was keenly interested not alone in the advancement of science, but also in the welfare of the patients of the Hospital. He was at all times interested in the affairs of New York, his native city, and was an outstanding figure in philanthropic and cultural fields. He was active in the foundation of the University Settlement Society, the Provident Loan Society, the Speyer School, the Ellin Prince Speyer Hospital for Animals and the Museum of the City of New York. He was also one of the founders of the American Museum of Safety and the Economic Club of New York. In all of these fields, he leaves behind him many achievements as evidence of having been what he wished to be known as, "a good citizen". His sincerity, humanity and integrity earned him the respect of all who knew him and he will long be remembered for his many good deeds.

DEW. M.

Seth Selig
October 31, 1897—November 2, 1941

"We loved him as a brother." So spoke one of his colleagues revealing the high esteem in which Seth Selig was held by his fellow-workers. His sudden demise at the early age of forty-four years terminated a very full life and an active and fruitful career. Although he had already reached the pinnacle of success in his chosen field and although a countless number of patients had benefited by his wise counsel and skillful surgery, undoubtedly, his *opus magnum* was yet to materialize as the result of his accumulated experience, his practical interpretation of clinical data and his scientific zeal. For this alone we selfishly regret his passing. Even more deeply felt is the void left by the departure of one who was also admired for his friendship, loyalty, and sincerity; for his great sense of humor and radiant optimism; for his honesty; for his clear vision and courage in maintaining his convictions when right, and in accepting another viewpoint when wrong. Yes, Seth Selig was, indeed, a credit to his profession.

The character and accomplishments of my most intimate friend is best reflected by the depth and sincerity of the sorrow exhibited by so many of his associates and friends in all walks of life. To know that he had reached his goal by perseverance, by strength of will, and by fair dealing enhances our respect for his memory and may well serve as a shining example to those who follow in his footsteps.

The various appointments he held, the societies to which he belonged, the problems he had solved or hoped to solve, and the new operations he had devised constitute an enviable record of achievement.

There is one more attribute which made Seth Selig so well thought of and worthy of emulation. It was his simple, wholesome philosophy pertaining to life and his work. He was indeed a good, trustworthy doctor with a fine understanding of human nature and a very thoughtful genial personality sharing it generously with others.

And so we bid farewell to our comrade and are thankful that we could travel part of the way with one who so deservedly was loved as a brother.

GORDON D. OPPENHEIMER

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Tertoma of the Pineal Body. J. R. GERSTLEY, J. KASANIN, AND E. LOWENHAUPT. J. Pediat. 17: 512-520, October 1940.

An account is presented of a child with an intracranial tumor which at autopsy proved a true teratoma of the pineal body. A spongioblastoma multiforme, a unilateral development within this tumor, invaded surrounding structures and spread widely throughout the brain. The child showed pubertas praecox, initial symptoms of pituitary cachexia, and finally signs characteristic of involvement of the quadrigeminate plate and the hypothalamus. The emotional changes in the child and their significance are discussed.

This case presents several aspects of unusual interest. It is the eighteenth reported teratoma of the pineal body. One part of the teratoma comprised a spongioblastoma multiforme which invaded widely, infiltrating the hypothalamus. The early diagnosis offered difficulty as a vague history and absence of signs suggested either encephalitis or schizophrenia. It was not until late that positive neurologic signs indicated the true condition. This case is of further significance in view of current neurologic theories (Grinker) which postulate the basal ganglia and hypothalamus as the seat of emotions. Some authors, notably Bailey, Buchanan, and Bucy, report uncontrollable temper tantrums in patients with tumors of similar location. Our patient had all the outward manifestations of depression without being aware of such an emotion. Thus, he was not actually depressed. Actual emotions in modern man have a rich ideational content. Therefore, we believe that we offer an added shred of evidence that the region of the third ventricle and hypothalamus may be concerned with the expression of emotion, and not with the actual emotion itself.

Uterotubal Insufflation as a Test for Tubal Patency, 1920 to 1940. I. C. RUBIN. Am. J. Obst. & Gynec. 40: 628, October 1940.

The method of uterotubal insufflation, which was developed at The Mount Sinai Hospital, has undergone gradual development from its incipency in 1919 to its present status as a precise and safe clinical nonsurgical test for determining tubal patency. Carbon dioxide, adopted as the gas of choice, has proved its usefulness and superiority over the years. Strict regard for clinical indications and contraindications and attention to the rules of technique are essential safeguards. The information derived from kymographic insufflation goes beyond the mere fact of tubal patency, yielding physiologic data not otherwise obtainable. It affords graphic records but, unlike hystero-graphy, no photographic films. With hysterosalpingography it shares the same limitation: namely, the necessity for correct interpretation which in the last analysis is an art acquired by ample critical experience. Without going into its comparative merits, it is fair to say that uterotubal insufflation in careful hands can be utilized without untoward immediate accidents or sequelae in all cases where it is properly indicated for diagnosis and therapy.

Pigmentation of the Face following X-ray Examination of the Jaw. O. L. LEVIN AND H. T. BEHRMAN. *J. A. D. A.* 27: 1599, October 1940.

The authors describe the development of pigmentation of the skin in a colored girl following a single dental roentgenogram. The pigmentation appeared without any preceding erythema or other subjective or objective symptoms. The pigmentation was reproduced experimentally in this patient by means of exposure to small fractional doses of x-ray. The importance of the biologic reaction rather than the roentgen dosage is stressed. The pigmentation is not permanent and will disappear within several months without any sequelae.

Certain Outstanding Trends in Gynecology During the Past Forty Years. R. T. FRANK. *Am. J. Obst. & Gynec.* 40: 574-577, October 1940.

Forty years ago transabdominal surgery was still in a formative stage. The outlook of surgery as well as gynecology was based on mechanical procedures as evidenced in the treatment of sterility and dysmenorrhea, and the imperfect plastic operations performed.

In the interim, diagnosis, knowledge of pathology and physiology has increased. The medical armamentarium has been enriched by the Wassermann reaction, blood transfusion, x-ray diagnosis and treatment, and the phenomenal development of endocrinology, to mention only a few.

Today, cure of gonorrhea and other venereal infections by hyperthermia and chemotherapy, the increasingly widespread use of the Manchester operation for prolapse, the recognition of mechanical sterility by means of the Rubin insufflation test, and the application of endocrinology to many functional diseases of the female has resulted in reduction of mortality, increase in frequency of cures, and accuracy of control.

The Gastro-Intestinal Manifestations of Shock. P. KLEMPERER, A. PENNER, AND A. I. BERNHEIM. *Am. J. Digest. Dis.* 7: 410, October 1940.

Numerous reports of focal erosions and ulcerations of the gastro-intestinal tract and observations of our material led us to the conclusion that despite the wide variety of clinical states in which these lesions have been observed at autopsy they have one physiological state in common, namely shock. The basic physiologic disturbance occurring in shock consists in a discrepancy between the volume of circulating blood and the capacity of the circulatory system, in which the former is too small to adequately fill the latter. We believe that the compensatory vaso-motor reactions which are called forth by any of the varied stimuli which may create the clinical state of shock, are concerned in the pathogenesis of these gastro-intestinal lesions. Experimental evidence is brought forth in support of this concept.

Contact Dermatitis from a Plastic Wrist-Band. O. L. LEVIN AND H. T. BEHRMAN. *J. Int. Med.* 9: 569, November 1940.

After wearing a bracelet made of transparent plastic, a plasticized flexible sheeting, a patient developed a localized dermatitis at all points where the bracelet was in direct contact with the skin. The modern utilization of plastics and synthetic materials as jewelry and wearing apparel should be duly considered when investigating the possible sources of a contact dermatitis.

Operations on the Phrenic Nerve. A. H. AUESER. *Am. J. Surg.* 50: 715, December 1940.

The author discusses the indications for paralysis of the hemi-diaphragm which is the only effect sought for by operations on the phrenic nerve. The anatomy of the phrenic nerve is described with special emphasis upon the various anomalies which occur and which are of great importance to the surgeon. The various types of opera-

tions which may be employed and the results which they achieve are given in table form. The technique of the various types of operations is given in detail and the complications which may occur either during operation or postoperatively are classified. Various tests for diaphragmatic paralysis are also enumerated. A bibliography of over eighty references is appended.

Lipoid Granulomatosis—Involving Middle Ear. H. ROSENWASSER. Arch Otolaryngol. 32: 1045, December 1940.

Lipoid granulomatosis (type Hand-Schuller-Christian disease) occurring in an adult and with diffuse involvement of the middle ear and temporal bone as the sole manifestation of the disease is uncommon. Although the clinical course, the roentgenographic findings and the results of the pathologic examination of material removed at operation, were consistent with the diagnosis of carcinoma of the middle ear, the favorable course for more than four years after operation was considered so unusual as to warrant a review of the microscopic sections. This resulted in the establishment of the diagnosis of lipoid granulomatosis.

Had these slides not been reviewed it is probable that the case would have been regarded as one of carcinoma involving the middle ear and petrous pyramid, cured for four years. The case also demonstrates the difficulty which was met in establishing a diagnosis even by the most highly trained pathologists. Furthermore it indicates an excellent therapeutic result, attributable apparently to the intensive use of roentgen rays.

Cerebral Abscess (Paradoxical) Accompanying Congenital Heart Disease: Report of Two Cases. I. S. WECHSLER AND A. KAPLAN. Arch. Int. Med. 66: 1282, December 1940.

The authors report two cases of cerebral abscess in congenital heart disease. Only twelve cases have been reported in the literature, and of the fourteen only three have been diagnosed during life. Generally the diagnosis of embolism or thrombosis is made. If the diagnosis can be made early and the abscess evacuated, there is the possibility that life can be saved. In doubtful cases pneumoencephalography may lead to the correct diagnosis. The point stressed is that, though rare, abscess of the brain can occur in congenital heart disease in the absence of a primary focus of infection.

INDEX OF VOLUME EIGHT

The (*) preceding the page number indicates an original article; the letters "ab" similarly placed indicate an abstract; "cp" signifies a clinical pathological conference report; "cnp", a clinical neuropathological conference report; "b", a book review. Author entries are made only for original articles.

- ABEL, H., et al.,** Organization of the blood bank at The Mount Sinai Hospital, *210
- Abramson, I.,** Resting blood flow and peripheral vascular responses in different portions of the extremities, *328
- Abscess, cerebral, (paradoxic) accompanying congenital heart disease,** ab1252
- lung, *922
- pulmonary, aerobic, the treatment of, *40
- brain, multiple, cnp1236
- Acetanilid poisoning,** ab252
- Acne vulgaris, present day conception and treatment of,** ab1170
- Adamantinoma of the hypophyseal duct,** *798
- Adenocarcinoma, papillary, of testis; recurrence six years after orchidec-tomy,** cp309
- Adrenal cortical carcinoma, the estro-genic reactions in,** *514
- Agenesis of the cerebellum,** *441
- Allergy, the problem of in rheumatic disease,** *991
- Amyotrophic lateral sclerosis, recovery in** ab1167
- Aneurysm of the heart, diagnosis of,** *469
- intracranial; their origin and clinical behavior in a series of verified cases, *547
- Angina pectoris, association of, or coronary thrombosis with mitral stenosis,** *754
- and cardiac infarction from trauma or unusual effort, ab63
- differentiation of coronary insufficiency, coronary occlusion and, *820
- and peptic ulcer syndrome, *422
- Aorta, the pathogenesis of coarctation of,** *520
- Aortic regurgitation, syphilitic aortitis with an electrocardiographic and autopsy survey at the Massachusetts General Hospital,** *1034
- Aphasia, transient global and hallucinatory episode in neurosyphilis,** *101
- Appendicitis, the severer forms of, acute, with special reference to the treat-ment of appendiceal abscess,** ab317
- Arnheim, E. E.,** Interstitial hernia, *139
- Arterial pressure in man, comparison of simultaneous indirect (auscultatory) and direct (intra-arterial) measure-ments of,** *1042
- Arteriosclerosis of the coronary arteries and the mechanism of their occlu-sion,** ab1170
- Atresia of mitral orifice and separation of left auricle and ventricle,** *737
- Aufses, A. H.,** Asymptomatic traumatic diaphragmatic hernia mistaken for pulmonary tuberculosis, *143
- Auricular fibrillation, paroxysmal, and flutter without signs of organic car-diac disease in two brothers, *765 and flutter, the mechanism of, *965 premature systoles, persistent, ob-served for 24 years, *476 wave (P) of the human electrocardio-gram in normal and pathological states, *502**
- Averbuck, S. H.,** Acute generalized post-operative peritonitis simulating coronary artery thrombosis, *335
- Aviation medicine,** *980
- BACILLARY** dysentery, chronic, transfusion of blood from artificially immunized donor in the treatment of, ab1168
- infections, the relationship of, to chronic intermittent diarrhea, ab318
- Baehr, G.,** Foreword, B. S. Oppenheimer Anniversary Volume, *320
- Barker, L. F.,** Brown-Sequard syndrome in association with tuberculous spondylitis and pulmonary silico-tuberculosis, *341
- Barnes, A. R., and Burchell, H. B.,** The significance of negative T waves in all three standard leads of the elec-trocardiogram, *346
- Bass, M. H.,** Paroxysmal tachycardia in very early infancy, *357
- Bassen, F., et al.,** Organization of the blood bank at The Mount Sinai Hospital, *210
- Batterman, R. C. and DeGraff, A. C.,** Persistent auricular premature sys-toles observed for 24 years, *476
- Beck, D.,** Pericarditis and subacute bac-terial endocarditis, *364
- Bender, M. B. and Wechsler, I. S.,** The neurological manifestations of peri-arthritis nodosa, *1071
- Benjamin, J. E., et al.,** Coronary artery disease, observations on dispensary patients, *376
- Berg, A. A. and Rosenthal, N.,** Ligation of the splenic artery for thrombo-cy-

- topenic purpura and congestive splenomegaly, *382
- Bernheim, A. I. and Penner, A., Some compensatory mechanisms in heart failure, *901
- Bernstein, S. S., Echinococcus cyst of the liver; prolonged course with operative removal and complicating thrombosis of the portal vein, *399
- Bick, E. M., Differential diagnosis of solitary cystic areas in bone, *1225
- Biliary tract disease and heart disease, relationships between, *1121
- Bladder, atonic, neurogenic, treatment of by transurethral resection, *645
- diverticulum, carcinoma development in, ^{cp}235
- Blood bank, organization of at The Mount Sinai Hospital, *210
- Blood flow, peripheral, in ten women exhibiting Graves' disease, *1051
- resting, and peripheral vascular responses in different portions of the extremities, *328
- Bloom, S. M., Early diagnosis of otitic meningitis in children, *98
- Bluestone, E. M., Selections from the notebook of a hospital administrator, *409
- Blumenthal, G., Obituary, *115
- Blumer, G., A note on the relationship between jaundice in pigs and jaundice in human beings, *418
- Blumgart, H. and White, P. D., Cessation of repeated pulmonary infarction and of congestive failure after termination of auricular fibrillation by quinidine therapy, *1095
- Boas, E. P. and Levy, H., Angina pectoris and the peptic ulcer syndrome, *422
- Bone, differential diagnosis of solitary cystic areas in, *1225
- multiple myeloma with cord involvement, ^{cp}232
- Braden, S., et al., See Goldblatt, H., *579
- Brain abscesses, multiple and incidental finding of hemangiomatous malformation of the midbrain, ^{cp}312
- Bronchopneumonia, clinical features, course, and complications of suppurative, in children, *29
- pleural complications of acute, suppurative and necro-suppurative, *45
- roentgen features of suppurative, *32
- suppurative and necro-suppurative in children, *26
- treatment of acute suppurative in children, *37
- Brown-Sequard syndrome in association with tuberculous spondylitis and pulmonary silico-tuberculosis, *341
- Bundle branch block, concerning the form of the QRS deflections of the electrocardiogram in, *1104
- Burchell, H. B. and Barnes, A. R., The significance of negative T waves in all three standard leads of the electrocardiogram, *346
- C**ANCER, breast, primary, the effect of roentgen therapy in, *606; conditions determining, *184; known causes of, *186; research, five years of, *771
- Capon comb growth, urinary excretion of, promoting substances in Graves' disease and myxedema and modifications following iodine and desiccated thyroid therapy, *811
- Carbohydrate and fat in the diet, effect of on uric acid excretion, ^{ab}61
- Carcinoma, adrenal cortical, the estrogenic reactions in, *514
- of cerebellum, metastatic, multiple, ^{cp}112
- of common bile duct, primary, ^{ab}120
- developing in a bladder diverticulum, ^{cp}235
- of esophagus, resection of, ^{cp}107
- of nasopharynx with extension to the petrous pyramid, ^{ab}1169
- Cardiac compression, and calcification of the pericardium, report and discussion of four cases, *1144
- disease in two brothers, paroxysmal auricular fibrillation and flutter without signs of organic, *765
- infarction and angina pectoris from trauma or unusual effort, ^{ab}63
- Cardiovascular disease, a note on the inheritance of, *482
- Cerebellum, agenesis of, *441
- Cerebral arteries, bilateral thrombosis of the posterior, *995
- circulation, clinical syndromes produced by temporary disturbances of, *612
- Chemotherapy, massive dose, of early syphilis by the intravenous drip method, ^{ab}120
- Christian, H. A., The kidneys in subacute streptococcus viridans endocarditis, *427
- Cohen, I., Agenesis of the cerebellum (verified by operation), *441
- Extradural varix simulating herniated nucleus pulposus, *136
- Coles, J. S., Reduction en masse of a strangulated hernia; operative cure, *178
- Colitis, chronic ulcerative, biophotometric studies in 30 cases, ^{ab}64
- Collateral coronary circulation, a quantitative method for determining, *933
- Colon, diverticulitis of the, with special reference to the surgical complications, ^{ab}1174
- Colostomy, a new spur-crushing clamp, ^{ab}120

- Colp, R., Surgical problems in the treatment of gastric ulcer, *447
and Klingenstein, P., Late sequelae of strangulated hernia with a report of two illustrative cases, *129
- Congestive failure, cessation of repeated pulmonary infarction and of, after termination of auricular fibrillation by quinidine therapy, *1095
- Conner, L. A., The heart in fat embolism, *454
- Contraceptive advice, the attitude of the psychoneurotic toward scientific, ^{ab}63
- Corcoran, A. C. and Page, I. H., Quantitative formulation of maximum urinary specific gravity, *459
- Cornea, absorption lines of the, ^{ab}118
- Coronary artery disease, observations on dispensary patients, *376
thrombosis, acute generalized post-operative peritonitis simulating, *335
insufficiency, the differentiation of angina pectoris, coronary occlusion and, *820
- Coronary occlusion, differentiation of angina pectoris, coronary insufficiency and, *820
rehabilitation following acute, ^{ab}1173
- spontaneous pneumothorax simulating acute, *89
thrombosis, the association of angina pectoris or, with mitral stenosis, *754
- Cortical area, human, producing repetitive phenomena when stimulated, ^{ab}1166
- Craniopharyngeoma, ^{enp}243
- Crawford, J. H., The diagnosis of aneurysm of the heart, *469
- Cryptorchidism, treatment with male sex hormone, ^{ab}248
- D**ACK, S., See Master, A. M., et al., *89, 820, 1232
and Sussman, M. L., The roentgenkymogram in myocardial infarction III. Cases with normal electrocardiograms, *1064
- Davids, A. H. and Rubin, I. C., Hypertension associating uterine fibroids; considered from viewpoint of etiological connection and surgical risk (based on a review of 500 cases), *987
- DeGraff, A. C. and Batterman, R. C., Persistent auricular premature systoles observed for 24 years, *476
- Diabetes mellitus in one of identical twins, ^{ab}320
insulin hypoglycemia and vascular accidents in, *953
pulmonary infection and necrosis, ^{ab}1173
- Dermatitis, contact, from a plastic wrist-band, ^{ab}1251
- Desoxycorticosterone, *1177
- Dolger, H., See Pollack, H. et al., *925
- Dooley, M. D., See Robb, J. S. et al., *946
- Druss, J. G. and Maybaum, J. L., Otitic infections due to the pneumococcus type III, *829
- Dublin, L. I. and Marks, H. H., A note on the inheritance of cardiovascular disease, results of insurance investigations, *482
- Duodenal ulcer following acute injury of the spinal cord, *868
- E**AR, neoplasms involving the middle, ^{ab}1171
- Echinococcus cyst of the liver, *399
- Eichelberger, L., See Leiter, L., *744
- Electrocardiogram, uterine, *805
with normal limb leads and with abnormality in only one of four precordial leads, *898
- Ellenberg, M., See Pollack, H. *925
- Embolism, fat, in the heart, *454
- Emerson, K., Jr. and Van Slyke, D. D., The nephrotic crisis, *495
- Empyema, putrid, without fetid sputum ("surprise empyema"), *892
scoliosis following, ^{ab}250
- Endocarditis, the kidneys in subacute streptococcus viridans, *427
- Estrogens, the, *269
prophylactic implantation of, following surgical and radium castration, *543
tubal contractility, effects upon, and the vaginal secretion in the menopause, ^{ab}1171
- Evans, W. F. and Stewart, H. J., The peripheral blood flow in ten women exhibiting Graves' disease, *1051
- Eyes, vaccinia of the, ^{ab}1172
- F**ALLOPIAN tubes, lipiodol granuloma in, ^{ab}248
- Feet, painful lesions of, *1216
- Feil H., The auricular wave (P) of the human electrocardiogram in normal and pathological states, *502
- Fibrillation, auricular, termination of by quinidine therapy, *1095
ventricular, transient, *1005
- Fibrosarcoma, huge, of the pleura, ^{enp}308
- Fishberg, A. M., The use of sulfonamides in renal insufficiency, *509
- Fisher, A. M., See Longcope, W. T., *784
- Fractures, pathological, management of, ^{ab}249
- Frank, R. T., The estrogens, *269
The estrogenic reactions in adrenal cortical carcinoma, *514
- Friedberg, C. K., The pathogenesis of coarctation of the aorta: a new theory, *520
- Friedman, B. et al., Therapeutic agents and renal implantations in experimental hypertension, *534

- GARLOCK, J. H.**, Suppurative tenosynovitis of the hand, *540
 and Lichtman, S. S., The present status of vitamin K therapy, *76
- Gastro-intestinal tract, acute perforations of, during hospital observation, *721
- Geist, S. H., et al., Prophylactic implantation of estrogens following surgical and radium castration, *543
- Ginandes, G. J., Treatment of acute suppurative bronchopneumonia in children, *37
- Glaubach, S., See Pick, E. P., *909
- Globus, J. H. and Schwab, J. M., Intracranial aneurysms; their origin and clinical behavior in a series of verified cases, *547
- Goiter, exophthalmic, management in a general hospital, ^{ab}249
- Goldblatt, H. et al., Studies on experimental hypertension XVI. The effect of hypophysectomy on experimental renal hypertension, *579
- Goldowsky, S. J., An unusual type of direct inguinal hernia, *167
- Gout, the use of high fat and high purine diets in the diagnosis of, *854
- Granulocytopenia caused by sulfapyridine in children, ^{ab}119
- Granulomatosis, lipoid, involving the middle ear, ^{ab}1252
- Grasping and sucking, ^{ab}317
- Graves' disease, peripheral blood flow in ten women exhibiting, *1051
 urinary excretion of capon comb growth promoting substances in, and myxedema and modifications following iodine and desiccated thyroid therapy, *811
- Greene, L. N. and Neuhoof, H., Direct hernia in the female, *155
- Grishman, A., See Master, A. M. et al., *820
- Gynecology, outstanding trends in, during past forty years, ^{ab}1251
- HAMBLÉN, E. C.**, Some clinical observations upon the metabolism and utilization of progesterone; their applications to gynecic practice, *1200
- Hamburger, W. W., Development of knowledge concerning the measurement and rhythm of the pulse (Herophilus, Galen, Carboliensis, Struthius, Galileo, Floyer), *585
- Harkavy, J., Vascular allergy II. Manifestations of polyvalent sensitization, *592
- Harris, W., The effect of roentgen therapy in primary cancer of the breast, *606
- Harrison, T. R., Clinical syndromes produced by temporary disturbances of the cerebral circulation, *612
- Heart, diagnosis of aneurysm of, *469
 disease, biliary tract disease, relationship between, *1121
 failure, compensatory mechanisms in, *901
 mechanism of, *668
 involvement of in sarcoidosis or Besnier-Boeck-Schaumann's disease, *784
 syphilitic, ^{cp}233
- Heidelberger, M., Complement titrations in human sera, *622
- Hemangiomas, malformation of the midbrain, multiple brain abscesses and incidental finding of, ^{cp}312
- Hematoma, spontaneous perirenal, *682
- Hemorrhoids, treatment of internal, by injection, ^{ab}62
- Hennell, H., Clinical features, course and complications of suppurative bronchopneumonia in children, *29
- Hernia, diaphragmatic, asymptomatic, traumatic, mistaken for pulmonary tuberculosis, *143
 congenital, report of a case with sudden death, ^{ab}318
 direct, in the female, *155
 inguinal, unusual type, *167
 femoral, incarcerated, containing adherent appendix, *175
 modification of Moschcowitz operation for, *125
 interstitial, *139
 in linea semilunaris, *164
 Richter's, strangulated, operative treatment by laparotomy, *181
 strangulated, late sequelae of, *129
 reduction en masse; operative cure, *178
 urinary bladder, *170
- Hernioplasty, inguinal, complete division of spermatic cord, *149
 puncture of external iliac artery and vein during, *152
- History of The Mount Sinai Hospital, I, *1239
- Hitzig, W. M., On mechanisms of inspiratory filling of the cervical veins and pulsus paradoxus in venous hypertension, *625
- Hormones, the female sex, ^{ab}63
- Hospital administrator, selections from the notebook of a, *409
- Hoyt, W. A., See Goldblatt, H. et al., *579
- Human sera, complement titrations in, *622
- Hydroxyl groups, methylation of, in triazines, *1032
- Hyman, A. and Leiter, H. E., A case of xanthine calculi, *84
 Treatment of atonic neurogenic bladder by transurethral resection, *645
- Hypertension, arterial, the nature of clinical and experimental, *3

- experimental XVI, studies on, *579
 therapeutic agents and renal im-
 plantations in, *534
 hemato-encephalic barrier; hyperten-
 sion of cerebrospinal fluid in hy-
 pertensive disease, ^{ab}252
 incidence of, in people 40 years of age
 and older, *1232
 relation of benign and malignant, *916
 uterine fibroids associating, *987
 Hyperthyroidism, the medical manage-
 ment of, ^{ab}1169
 Hypophyseal duct, adamantinoma of
 the, *798
 Hypophysectomy, the effect of, on ex-
 perimental renal hypertension, *579
- INFARCTION**, factors affecting the
 outcome in acute, of the myocar-
 dium, *1104
 Inspiratory filling, mechanism of, of the
 cervical veins and pulsus paradoxus
 in venous hypertension, *625
 Insulin hypoglycemia and vascular acci-
 dents in diabetes mellitus, *953
 Iodine, blood, in the period after thy-
 roidectomy, *1027
 therapy, urinary excretion of capon
 comb growth promoting sub-
 stances in Graves' disease and
 myxedema and modifications fol-
 lowing, and desiccated thyroid
 therapy, *811
 Isaacs, R., Dynamics of symptom pro-
 duction in splenomegaly, *651
- JAFFE**, H. L., See Master, A. M. et al.,
 *820
 Janeway lecture, the nature of clinical
 and experimental arterial hyperten-
 sion, *3
 Jarcho, S., An early case of horseshoe
 kidney, *656
 Jarman, J., See Friedman, B. et al., *534
 Jaundice, note on the relationship be-
 tween, in pigs and in human beings,
 *418
 relation of anoxemia to, in lobar pneu-
 monia, *703
 Jolliffe, N., The neuro-psychiatric mani-
 festations of vitamin deficiencies,
 *658
- KAHN**, J. R., See Goldblatt, H., et al.,
 *579
 Kalter, H. H., See Master, A. M., et al.,
 *89
 Katz, L. N., Mechanism of heart failure,
 *668
 Kayland, S., See Prinzmetal, M., et al.,
 *933
 Keefer, C., Spontaneous perirenal hema-
 toma, *682
 Keith, N. M., The significance of plasma
 and blood volume studies in clinical
 medicine, *692
- Kidney, aseptic infarction of, *1220
 early case of horseshoe, *656
 evaluation of roentgenography of sur-
 gically exposed, in the treatment
 of renal calculi, ^{ab}319
 extracts ("Renin") and the production
 of cardiac and gastro-intestinal
 hemorrhages and necrosis in dogs
 with abnormal renal circulation,
 *744
 in subacute streptococcus viridans en-
 docarditis, *427
 King, F. H. and Leslie, A., Relation of
 anoxemia to jaundice in lobar pneu-
 monia, *703
 Klemperer, P. and Tedeschi, C., Pleural
 mesothelioma, *710
 Klingenstein, P. and Colp, R., Late
 sequelae of strangulated hernia with
 a report of two illustrative cases,
 *129
 and Tuchman, L. R., Acute perfora-
 tions of the gastro-intestinal tract
 during hospital observation, *721
 Koller, C., Ocular tension and intraocu-
 lar circulation, *731
 Kramer, B., Vitamin D therapy, *188
 Krumbhaar, E. B., A congenital cardiac
 anomaly; atresia of mitral orifice
 and separation of left auricle and
 ventricle, *737
- LANDEN**, M., See Benjamin, J. E. et
 al., *376
 Landt, H., See Benjamin, J. E. et al.,
 *376
 Leiter, H. E. and Hyman, A., A case of
 xanthine calculi, *84
 Treatment of atonic neurogenic blad-
 der by transurethral resection,
 *645
 Leiter, L. and Eichelberger, L., Pressor
 kidney extracts ("Renin") and the
 production of cardiac and gastro-
 intestinal hemorrhages and necrosis
 in dogs with abnormal renal circula-
 tion, *744
 Leslie, A., See King, F. H., *703
 Leucopenic states, a new method for the
 treatment of, *895
 Levine, S. A., The association of angina
 pectoris or coronary thrombosis
 with mitral stenosis, *754
 Levy, H. and Boas, E. P., Angina pec-
 toris and the peptic ulcer syndrome,
 *422
 Levy, J. H., Herniation of the urinary
 bladder, *170
 Levy, R., Paroxysmal auricular fibrilla-
 tion and flutter without signs of
 organic cardiac disease in two
 brothers, *765
 Lewisohn, R., Five years of cancer re-
 search, *771
 Libman, E., Notes on clinical observa-
 tions and methods, II, *777

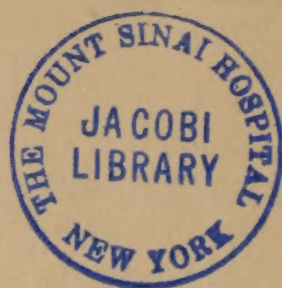
- Lichtman, S. S. and Garlock, J. H., The present status of vitamin K therapy, *76
- Lichtwitz, L., Nephrosis and the 'nephrotic syndrome', *782
- Lilienthal, H., Alex Moschcowitz, my friend, *121
- In the beginning, *321
- Liver, influence of protein metabolism on the distribution of nitrogen compounds in the, *909
- subacute yellow atrophy of the, ^{ab}1167
- toxic cirrhosis of, ^{cp}52
- Longcope, W. T. and Fisher, A. M., Involvement of the heart in sarcoidosis or Besnier-Boeck-Schaumann's disease, *784
- Lung abscess, *922
- interlobar perforated, ^{ab}319
- Lymphogranuloma, venereal, treatment with sulfanilamide, ^{ab}251
- Lymphosarcoma of stomach, *305
- M**acCALLUM, W. G., Adamantinoma of the hypophyseal duct, *798
- Magasanik, B., See Silver, S., *1027
- Malaria, inoculation, and drug addiction, *998
- Mann, H. and Mayer, M. D., The uterine electrocardiogram, *805
- Margoles, C., See Prinzmetal, M. et al., *933
- Marine, D. and Rosen, S. H., Urinary excretion of capon comb growth promoting substances in Graves' disease and myxedema and modifications following iodine and desiccated thyroid therapy, *811
- Marks, H. H., See Dublin, L. I., *482
- Master, A. M., et al., Incidence of hypertension in people 40 years of age and older, *1232
- Nomenclature of coronary artery disease; the differentiation of angina pectoris, coronary insufficiency and coronary occlusion, *820
- Spontaneous pneumothorax simulating acute coronary occlusion, *89
- Maybaum, J. L. and Druss, J. G., Otitic infections due to the pneumococcus type III, *829
- Mayer, M. and Vogel, P., An intra-group hemolytic transfusion reaction due to the Rh agglutinin as a result of isoimmunization in pregnancy, *300
- and Mann, H., The uterine electrocardiogram, *805
- Maynard, E. P., Pioneers in cardiovascular syphilis, *841
- McEwen, C., The use of high fat and high purine diets in the diagnosis of gout, *854
- Meckel's diverticulum, ulcer in, *1118
- Mencher, W. H., Complete division of the spermatic cord in conjunction with inguinal hernioplasty, *149
- Meningitis, otitic, early diagnosis in children, *98
- Mesothelioma, pleural, *710
- Mindlin, E. P. and Zucker, J. M., Cystic tumor of the fourth ventricle, *92
- Minsky, H., Experimental holes in the retina, *863
- Mitral stenosis, the association of angina pectoris or coronary thrombosis with, *754
- Moolten, S. E., Duodenal ulcer following acute injury of the spinal cord, *868
- Moschcowitz, E., The validity of nephrosis as a nosological concept, *878
- Moschcowitz operation for femoral hernia, modification of, *125
- Mycocardium, factors affecting the outcome in acute infarction, *1104
- Myxedema, urinary excretion of capon comb growth promoting substances in Graves' disease, and modifications following iodine and desiccated thyroid therapy, *811
- N**EPHRITIS and nephrosis in children, the prognosis of, ^{ab}1167
- Nephrosis and the 'nephrotic syndrome', *782
- validity of, as a nosological concept, 878
- Nephrotic crisis, *495
- Neuhof, H., A modification of the Moschcowitz operation for femoral hernia, *125
- Pleural complications of acute suppurative and necro-suppurative bronchopneumonia, *45
- Putrid empyema without fetid sputum ('surprise' empyema), *892
- Strangulated Richter's hernia; operative treatment by laparotomy, *181
- and Greene, L. N., Direct hernia in the female, *155
- Neurospiroglioblastoma, cerebral hemisphere, left, ^{cp}57; right, ^{cp}54
- O**CULAR tension and intraocular circulation, *731
- Oppenheimer, G. D., Aseptic infarction of the kidney, *1220
- Otitic infections due to pneumococcus type III, *829
- Ottenberg, R., A new method for the treatment of leucopenic states, *895
- Ovarian tumors, experimental, ^{ab}251
- Oxygen, heavy, exchange reactions in proteins and amino acids, ^{ab}252
- P**AGE, I. H., The Edward Gamaliel Janeway Lecture. The nature of clinical and experimental arterial hypertension, *3
- and Corcoran, A., Quantitative formulation of maximum urinary specific gravity, *459

- Pardee, H. E. B., Electrocardiograms with normal limb leads and with abnormality in only one of four precordial leads, *898
- Penner, A. and Bernheim, A. I., Some compensatory mechanisms in heart failure, *901
- Periarthritis nodosa, the neurological manifestations of, *1071
- Pericarditis, rheumatic, with effusion treated with salicylates, ^{ab}1172 and subacute bacterial endocarditis, *364
- Pericardium, calcification of and chronic cardiac compression; report and discussion of four cases, *1144
- Peripheral vascular disease, physical measures in the treatment of, *1128
- Peritonitis, acute generalized postoperative, simulating coronary artery thrombosis, *335
experimental, ^{ab}250
- Perspiration, insensible, in children, ^{ab}117
- Phrenic nerve, operation on, ^{ab}1251
- Pick, E. P. and Glaubach, S., The influence of protein metabolism on the distribution of nitrogen compounds in the liver, *909
- Pickering, G. W., The relationship of benign and malignant hypertension, *916
- Pigmentation of face following x-ray examination of jaw, ^{ab}1251
- Pineal body, teratoma of, ^{ab}1250
- Plasma and blood volume, the significance of, *692
- Pneumonia, lobar, relation of anoxemia to jaundice, *703
- Pneumococcus, type III, otitic infections due to, *829
- Pneumonolysis, extrapleural, in the treatment of pulmonary tuberculosis, ^{ab}64
- Pneumothorax, spontaneous, simulating acute coronary occlusion, *89
- Poll, D., Lung abscess, *922
- Pollack, H. et al., Postoperative precipitation of vitamin B complex deficiencies, *925
- Polycythemia vera, thrombo-angiitis obliterans and, *1021
- Potassium chloride, displacement of the RS-T segment by, *946
- Prinzmetal, M., et al., A quantitative method for determining collateral coronary circulation, *933
- Progesterone, some clinical observations upon the metabolism and utilization of, *1200
- Prostatectomy, transurethral, results of, ^{cp}109
- Protein metabolism, the influence of, on the distribution of nitrogen compounds in the liver, *909
- Pruritus caused by leukoplakia-kraurosis vulvae, tattooing (puncturation) with mercury sulfide for the treatment of intractable, ^{ab}1173
- ani, perinei, tattooing (puncturation) with mercury sulfide and other chemicals for the treatment of, ^{ab}1171
- treatment by tattooing with mercury sulfide, ^{ab}1166
- Puberty, menstruation, pregnancy, ^{ab}318
- Pulmonary infarction, cessation of repeated, and of congestive failure after termination of auricular fibrillation by quinidine therapy, *1095
- silico-tuberculosis, Brown-Sequard syndrome in association with tuberculous spondylitis and, *341
- suppuration, non-putrid, roentgen aspects of, ^{ab}1174
- Pulse, development of knowledge concerning the measurement and rhythm of, *585
- Pulsus paradoxus, on mechanisms of inspiratory filling of the cervical veins and, in venous hypertension, *625
- Q**UINIDINE therapy, cessation of repeated pulmonary infarction and of congestive failure after termination of auricular fibrillation by, *1095
- R**ABIN, C. B., Roentgen features of suppurative bronchopneumonia, *32
- Raynaud's disease, vitamin therapy in, *284
- Recklinghausen's disease, ^{ab}1166
- Reiner, M., Manual of clinical chemistry, ^b1176
- Renal circulation, pressor kidney extracts and the production of cardiac and gastro-intestinal hemorrhages and necrosis in dogs with abnormal, *744
- hypertension, the effect of hypophysectomy on experimental, *579
- implantations, therapeutic agents and, in experimental hypertension, *534
- Retina, experimental holes in the, *863
- Rh agglutinin as a result of isoimmunization in pregnancy, an intragroup hemolytic transfusion reaction due to the, *300
- Rheumatic disease, the problem of allergy in, *991
- Rickets and tetany, treatment of by parenteral administration of one massive dose of vitamin D, ^{ab}1169
- treatment with single massive dose of vitamin D, ^{ab}61
- Robb, J. S., et al., Displacement of the RS-T segment by potassium chloride, *946
- Robb, R. C., See Robb, J. S., et al., *946
- Roentgen therapy, the effect of in primary cancer of the breast, *606

- Roentgenkymogram in myocardial infarction III. Cases with normal electrocardiograms, *1064
- Root, H. F. and Styron, C. W., Insulin hypoglycemia and vascular accidents in diabetes mellitus, *953
- Rosen, S. Otogenous tetanus, *96
- Rosen, S. H., See Marine, D., *811
- Rosenthal, N., et al., The organization of the blood bank at The Mount Sinai Hospital, *210
- and Berg, A. A., Ligation of the splenic artery for thrombocytopenic purpura and congestive splenomegaly, *382
- Roth, I. R., The mechanism of auricular flutter and fibrillation. An historical survey, *965
- Rous, P., The William Henry Welch Lectures. I. The conditions determining cancer, *184
- II. The known causes of cancer, *186
- Rowntree, L. G., Aviation medicine, *980
- Rubin, I. C. and Davids, A. M., Hypertension associating uterine fibroids; considered from viewpoint of etiological connection and surgical risk (based on a review of 500 cases), *987
- Rubin test, the effect of castration on tubal contractions of the rabbit as determined by the, ^{ab}118
- SACHS, B.**, Be an optimist, *323
- Sacroccygeal cysts and sinuses, radiation therapy for recurrent, ^{ab}1174
- Salmon, U. J., See Geist, S. H. et al., *543
- Sarcoidosis or Besnier - Boeck - Schau-mann's disease, involvement of the heart in, *784
- Sarot, I. A., Hernia in the linea semi-lunaris, *164
- Schick, B., The problem of allergy in rheumatic disease, *991
- Schick reactions, bullous, their occurrence during acute infectious diseases, ^{ab}1172
- Schlieve, K., Bilateral thrombosis of the posterior cerebral arteries, *995
- Schoenbach, E. B. and Spingarn, C. L., Inoculation malaria and drug addiction, *998
- Schwab, J. M., See Globus, J. H., *547
- Schwartz, S. P., Transient ventricular fibrillation, *1005
- Sclerosis, amyotrophic lateral, ^{enp}238
- Scoliosis following empyema, ^{ab}250
- Scurvy due to prolonged Sippy diet or purpura due to skeletal metastases from primary gastric carcinoma of five years' duration, ^{enp}50
- Sedimentation time, the value of in suppurations of the anorectal tissues, ^{ab}1168
- Seelig, M. G., An appreciation of Dr. Alexis Victor Moschowitz, *123
- Seley, G. P., Incarcerated femoral hernia containing adherent appendix, *175
- Puncture of the external iliac artery and vein during inguinal hernioplasty, *152
- Selig, S., Painful lesions of the feet, *1216
- Obituary, *1249
- Serum calcium in the newborn, ^{ab}61
- Shock, gastro-intestinal manifestations of, ^{ab}1251
- Sigmoidoscopic perforation, the conservative management of, ^{ab}1175
- Silbert, S., Thrombo-angiitis obliterans and polycythemia vera, *1021
- Silver, S., and Magasanik, B., The blood iodine in the period after thyroidectomy, preliminary report, *1027
- Snapper, I., Chinese lessons to western medicine, ^b1176
- Snell, A. M., The analogues of vitamin K; their clinical usefulness, *67
- Sobotka, H., The biological role of the steroids and their bearing on clinical medicine, *255
- and Bloch, E., Methylation of hydroxyl groups in triazines; studies on triazines, *1032
- Speyer, J., Obituary, *1248
- Spiegel, R., Vitamin therapy in Raynaud's disease, preliminary report, *284
- Spinal cord, extradural varix simulating herniated nucleus pulposus, *136
- duodenal ulcer following acute injury of, *868
- Spingarn, C. L., and Schoenbach, E. B., Inoculation malaria and drug addiction, *998
- Splenic artery, ligation of, for thrombocytopenic purpura and congestive splenomegaly, *382
- Splenomegaly congestive, ligation of the splenic artery for thrombocytopenic purpura and, *382
- dynamics of symptom production in, *651
- Sprague, H. B., Syphilitic aortitis with aortic regurgitation—an electrocardiographic and autopsy survey at the Massachusetts General Hospital, *1034
- Stats, D., Transient global aphasia and hallucinatory episodes in neurosyphilis, *101
- Steele, J. M., Comparison of simultaneous indirect (auscultatory) and direct (intra-arterial) measurements of arterial pressure in man, *1042
- Steroids, the biological role of, and their bearing on clinical medicine, *255
- Stewart, H. J. and Evans, W. F., The peripheral blood flow in ten women exhibiting Graves' disease, *1051

- Stomach, lymphosarcoma of, *305
- Strauss, I., Masseter and temporal muscle tenderness in syphilitic trigeminal neuritis, *1060
- Styron, C. W. and Root, H. F., Insulin hypoglycemia and vascular accidents in diabetes mellitus, *953
- Subacute bacterial endocarditis, pericarditis and, *364
- self - observations and psychologic reactions of medical student A.S. R. to onset and symptoms of, *1079
- Subdural hematoma, traumatic, further notes, ^{ab}119
- Sulfanilamide, observations concerning absorption from large intestine in man; an experimental study, ^{ab}62
- studies on the absorption of from the large intestine; results following the administration of suppositories, ^{ab}1174
- therapy, varicelliform eruption resulting from, ^{ab}319
- use of in surgery of the colon and rectum, ^{ab}63
- value of in otogenous infections, ^{ab}64
- Sulfapyridine, granulocytopenia caused by, in children, ^{ab}119
- Sulfonamides, the use of in renal insufficiency, *509
- Sussman, M. L. and Dack, S., The roentgenkymogram in myocardial infarction III. Cases with normal electrocardiograms, *1064
- Sweat, the chemical content of, an experimental study, ^{ab}1170
- Syphilis, cardiovascular, pioneers in, *841
- ocular, treatment of, ^{ab}1168
- of the stomach, ^{ab}1175
- Syphilitic aortitis with aortic regurgitation—an electrocardiographic and autopsy survey at the Massachusetts General Hospital, *1034
- trigeminal neuritis, masseter and temporal muscle tenderness in, *1060
- T WAVES**, the significance of negative, in all three standard leads of the electrocardiogram, *346
- Tachycardia, paroxysmal, in very early infancy, *357
- Tedeschi, C., See Klemperer, P., *710
- Tenosynovitis, suppurative, of the hand, *540
- Tetanus, otogenous, *96
- Thomas, A., Suppurative and necrosuppurative bronchopneumonia in children, *26
- Thoracoplasty, partial (with extrafascial apicolysis) and contralateral oleothorax, ^{ab}120
- Thorn, G. W., Desoxycorticosterone, *1177
- Thrombo-angiitis obliterans and polycythemia vera, *1021
- Thrombocytopenic purpura and congestive splenomegaly, ligation of the splenic artery for, *382
- Thrombosis, cerebral arteries, posterior, bilateral, *995
- coronary artery, acute generalized postoperative peritonitis simulating, *335
- portal vein, echinococcus cyst of the liver; prolonged course with operative removal and complicating, *399
- Thyroid therapy, desiccated, urinary excretion of capon comb growth promoting substances in Graves' disease and myxedema and modifications following iodine and, *811
- Thyroidectomy, the blood iodine in the period after, *1027
- Touroff, A. S. W., The treatment of aerobic pulmonary abscess, *40
- Trachea, sarcoma of, ^{ab}249
- Traction, movable carrier, ^{ab}238
- Tragerman, L., See Prinzmetal, M. et al., *933
- Triazines, studies on, *1032
- Tuberculin patch test (Vollmer and Lederle), evaluation of, ^{ab}64
- Tuberculosis, allergometric study, ^{ab}249
- bone; basal metabolism of tuberculous children, ^{ab}250
- and joints, visceral complications in, ^{ab}117
- childhood, basal metabolism in; children with pneumothorax, ^{ab}251
- peri-anal, ^{ab}118
- pulmonary, extrapleural pneumonolysis in the treatment of, ^{ab}64
- mistaken diagnosis of, *143
- Tuberculous children, basal metabolism of, ^{ab}118
- spondylitis, Brown-Sequard syndrome in association with, and pulmonary silico-tuberculosis, *341
- Tuchman, L. R. and Klingenstein, P., Acute perforations of the gastrointestinal tract during hospital observation, *721
- Tumor, cystic of the fourth ventricle, *92
- Turner, J., Dr. B. S. Oppenheimer's contributions to postgraduate medical education, *326
- Typhoid vaccine, temperature changes in skin and muscle of lower extremities following intravenous injections of, ^{ab}62
- ULCER**, duodenal following acute injury of the spinal cord, *868
- gastric, surgical problems in the treatment of, *447
- in Meckel's diverticulum; unique roentgenologic findings, *1118
- peptic syndrome and angina pectoris, *422

- Uremia due to prostatic fibroadenoma of four years' duration; results of transurethral prostatectomy, ^{cp}109
- Ureteropelvic anastomosis following avulsion, ^{ab}317
- Uric acid excretion, effect of carbohydrate and fat in the diet on, ^{ab}61
- Urinary specific gravity, quantitative formulation of maximum, *459
- Urologic disease, the intestinal phase, ^{ab}117, 119, 1167
- Uterine electrocardiograms, *805
fibroids, hypertension associating, *987
- Uterotubal insufflation as a test for tubal patency, ^{ab}1250
- VAN SLYKE, D. D.** and Emerson, K., Jr., The nephrotic crisis, *495
- Vascular accidents and insulin hypoglycemia in diabetes mellitus, *953
- allergy II. Manifestations of polyvalent sensitization, *592
- Venous hypertension, on mechanisms of inspiratory filling of the cervical veins and pulsus paradoxus in, *625
- Vitamin A deficiency in children, cutaneous manifestations of, ^{ab}320
- B complex deficiencies, postoperative precipitation of, *925
- C determinations in children by intradermal injection, ^{ab}250
- D therapy, *188
treatment of rickets and tetany with single massive dose, ^{ab}61
- deficiencies, the neuro - psychiatric manifestations of, *658
- K, the analogues of; their clinical usefulness, *67
therapy, the present status of, *76
therapy in Raynaud's disease, *284
- Vogel, P., See Rosenthal, N. et al, *210
- and Mayer, M. D., An intra-group hemolytic transfusion reaction due to the Rh agglutininogen as a result of isoimmunization in pregnancy, *300
- WALTER, R. I.**, See Geist, S. H. et al., *543
- Wasserman, L. R., See Rosenthal, N. et al., *210
- Wechsler, I. S. and Bender, M. B., The neurological manifestations of periarteritis nodosa, *1071
- Weiss, S., Self-observations and psychologic reactions of medical student A.S.R. to the onset and symptoms of subacute bacterial endocarditis, *1079
- White, P. D. and Blumgart, H. L., Cessation of repeated pulmonary infarction and of congestive failure after termination of auricular fibrillation by quinidine therapy, *1095
- Willius, F. A., Factors affecting the outcome in acute infarction of the myocardium, *1104
- Wilson, F. N., Concerning the form of the QRS deflections of the electrocardiogram in bundle branch block, *1110
- Winkelstein, A., Ulcer in Meckel's diverticulum, unique roentgenologic findings, *1118
- Wolferth, C. C., Relationships between biliary tract disease and heart disease, *1121
- Wright, I. S., Physical measures in the treatment of peripheral vascular disease, *1128
- XANTHINE** calculi, *84
- YARNIS, H.**, Lymphosarcoma of the stomach, *305
- Yater, W. M., Calcification of the pericardium and chronic cardiac compression; report and discussion of four cases, *1144
- ZEMAN, F.**, Old age in ancient Egypt. A contribution to the history of geriatrics, *1161
- Zucker, J. M. and Mindlin, E. P., Cystic tumor of the fourth ventricle, *92



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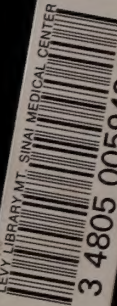
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